Amsterdam UMC

Amsterdam Gastroenterology Endocrinology Metabolism

AGEM Annual report 2023

Colophon

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Contents

Directors looking back

The directors reflect on the past year, during which the initial six years of the AGEM research institute were evaluated according to the Strategy Evaluation Protocol (SEP). The process towards this evaluation included interviewing AGEM researchers about their thoughts and subsequently writing a self-evaluation report. “It was not only fun, bringing our researchers together to talk, but it also turned out to be exceptionally useful”, Stan van de Graaf says, “it brought us closer together and it helped identify areas of improvement”. “I agree, and it helped me to get a comprehensive idea of the institute, at breakneck speed”, Anita Boelen chuckles.

November 29 and 30 marked the days of the official visit of the international SEP committee. The extensive preparation towards these days would not have been possible without policy officer Maartje Schots. “But, unfortunately for us”, Stan states, “she encountered her dream job in South Sudan and was not present during the visitation”. “Thankfully, we found a replacement just in time, namely Esther de Regt”, Anita adds, “we are very glad that the collaboration with her is equally pleasant”. The visitation came to be a success. “Although we were already proud of our institute after finishing our self-evaluation report, the initial results of the official evaluation were astonishing!”, Stan smiles. “I could not agree more”, Anita adds, “I did not know what to expect at first, but it turned out to be a very fun day with both positive and useful feedback from the committee members”.

The SEP evaluation was not the only event of 2023; as always the Tager lectures, the PhD candidate course and the annual retreat were well attended and well received. “Apart from facilitating networking through these events, we were very happy to support our AGEM researchers financially through our innovation grants and our talent development grants, and to have helped four master students to develop their skills further during an internship abroad”, Stan states. “And of course to have helped fund the printing of all those PhD theses”, Anita smiles.

The significance and value of the researchers at AGEM was underscored by their various successes, such as the €9.4M NWO grant that was awarded to the MenoPause consortium led by prof. dr. Peter Bisschop, the Academy Medal from KNAW that was given to prof. dr. Carla Hollak, and the fact that the metabolic disease ALD is now officially part of the Dutch newborn screening thanks to the efforts of dr. Stephan Kemp, dr. Marc van Engelen, dr. Monique Albersen and the Screening Lab of Amsterdam UMC. “I also remember the symposium for the launch of the new nutrition textbook ‘Leerboek Voeding’, that was a proud moment”, Stan adds.

“On top of that, it is exciting to have seen an increase of social impact initiatives”, Anita exclaims, “such as the My Health Buddy application and the further development of the StoMakker application”. “And our business developer Ric van Tol has proven to be a valuable asset in identifying new opportunities for collaboration, particularly with private partners”, Stan adds. Ric, together with policy officer Eva Dirkx, also played a key part in strengthening the role of AGEM within the Amsterdam UMC Food for Life initiative. “After a successful PI event in October, we feel confident about the central position of the AGEM research within this project”, Stan states. “And by gearing our 2024 innovation grant towards this same theme, we hope to stimulate collaboration between our researchers”, Anita adds.

Another pivotal moment of the last year was the strategy meeting with all the AGEM affiliated department heads in October. “Preceding this meeting, Anita and I set out to get to know all the department heads personally, to increase involvement and to foster a feeling of belonging”. “I definitely think that was a fruitful undertaking. We cannot plan our future without considering the strategy of the individual departments that are linked to our institute”, Anita explains.

Apart from feeling proud of the developments of the research institute in 2023, the directors look back on a year filled with fun. “Making the research institute into a success takes quite a lot of time, from both directors and policy officers, but due to the fun team dynamics, this was always worth it!” Anita concludes. “Definitely”, Stan adds, “and I hope you can carry this positivity into 2024, with my successor Nanne de Boer!”

Prof. dr. Anita Boelen and Prof. dr. Stan van de Graaf

Dr. Nanne de Boer

Gastroenterologist at the Department of Gastroenterology and Hepatology

Nanne will become Anita's co-director from 2024 onwards. He was already familiar with the AGEM research institute, as he works closely with Gerd Bouma, a previous AGEM director. This resulted in a positive view of the institute and enthusiasm about the opportunities thereof, which made the decision to become the next co-director an easy one.

Research Board 2023

The AGEM research board consists of the AGEM directors, nine members (at least one representative from each of the three AGEM research programs) and two AGEM policy officers. The research board meets approximately once per two months and discusses the AGEM policy.

The AGEM research board 2023

New to the AGEM Research Board 2023

Esther de Regt

Since September 2023, Esther de Regt joined the AGEM research board as AGEM policy officer. From a young age, Esther had an interest in all things living, which lead to her obtain her bachelor's degree in Biology. Intrigued by the research, but also interested in taking a different approach, she chose to obtain a master's degree in Biology & Science Communication and Society. The intersection between science and society, and between researchers and the general public awakened a new curiosity in her. Policy is a clear example of such an intersection, which is how Esther ended up as a policy officer at AGEM.

What I want to achieve with the AGEM research institute…

I am hoping to help AGEM reach their strategic aims in the following years, in part supplemented by the advice that will follow from the Strategy Evaluation Protocol (SEP). Furthermore, I expect to play a role in involving and connecting the AGEM researchers, thus creating an even stronger sense of belonging. Apart from inside the institute, my ambition is to strengthen our communication outwards, in specific towards the general public. Ultimately, the general public is the target group of all the research done at this institute, which underlines the importance of educating them on all current affairs.

AGEM directors 2023

Prof. dr. Anita Boelen

Department of Clinical Chemistry, Endocrine Laboratory

Professor of Thyroid Hormone Metabolism, in particular molecular and diagnostic aspects
Specialization: Thyroid hormone, neonatal screening
Research subject: The role of thyroid hormone metabolism in innate immune cells and the pathogenesis of congenital central hypothyroidism

Prof. dr. Stan van de Graaf

Tytgat Institute for Liver and Intestinal Research & Department of Gastroenterology and Hepatology

Professor of Experimental Hepatology and Metabolism
Specialization: Biochemistry/Physiology
Research subject: Targeting metabolite dynamics to treat metabolic and liver diseases

AGEM Research Board members 2023

Dr. Anje te Velde

Tytgat Institute for Liver and Intestinal Research & Department of Gastroenterology and Hepatology

Specialization: Immunology
Research subject: Study of chronic intestinal inflammation (inflammatory bowel disease, IBD): pathophysiology and therapeutic interventions.

Prof. dr. Annemieke Heijboer

Endocrine Laboratory & Department of Clinical Chemistry

Professor of Endocrine Laboratory Medicine
Specialization: Endocrinology/Clinical Chemistry
Research subject: To study physiology and pathophysiology within the field of endocrinology and to make the translation into endocrine diagnostics including the use of biomarkers.

Prof. dr. Annet Bosch

Department of Pediatric Metabolic Diseases

Professor of Pediatrics, Metabolic Disease
Specialization: Metabolic Diseases
Research subject: Diagnosis and Treatment of Galactosemia, Phenylketonuria, Riboflavin Transporter Deficiencies

Dr. Richard IJzerman

Department of Endocrinology

Internist endocrinologist
Specialization: Endocrinology, diabetes
Research subject: the influence of the hormonal and microbiota gut-brain axis on the regulation of food intake and the development of obesity

Dr. Hilde Herrema

Department of Experimental Vascular Medicine

Assistant professor
Specialization: Cardiometabolic disease
Research subject: Translational and integrative research into development of obesity, diabetes and fatty liver disease. Gut microbiome.

Dr. Joris Erdmann

Department of Surgery

Hepatobiliary and pancreatic surgeon
Specialization: Surgery
Research subject: To study liver function, regeneration and failure within the field of liver surgery.

Prof. dr. Noam Zelcer

Department of Medical Biochemistry

Professor of Molecular regulation of metabolism
Specialization: (Post)transcriptional regulation of lipid metabolism
Research subject: The regulation of lipid metabolism and the role this has in NAFLD and CVD.

Dr. Joep Derikx

Department of pediatric surgery

Pediatric surgeon
Specialization: neonatal abdominal surgery and pediatric thyroid gland surgery
Research subject: studying the pathophysiological consequences of intestinal anastomotic healing and disturbed healing; neonatal gut maturation and inflammation; develop markers that can be used to diagnose intestinal damage.

Dr. Stephan Kemp

Department of Clinical Chemistry

Associated professor
Specialization: inherited neurometabolic diseases
Research subject: lipid metabolism and neurotoxicity with a focus on X-linked adrenoleukodystrophy

AGEM office 2023

Dr. Eva Dirkx-Beuling

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)

Policy officer AGEM
PhD-thesis: GATA transcription factors and the regulation of intestinal development, differentiation and function.

MSc. Maartje Schots

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)

Policy officer AGEM
MSc. International Development / Global Health

MSc. Esther de Regt

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM)

Policy officer AGEM
MSc. Biology & Science Communication and Society

Dr. Ric van Tol

Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) and Innovation Exchange Amsterdam (IXA)

Business Development & Innovation Strate gy
Specialization: Nutrition and GI Health, Industrial Research Management

Science Impressions 2023

To give an impression of the research conducted at the AGEM research institute, seven couples of young investigators and their supervisors were invited to present the research projects they worked on in 2023.

Dietary therapy for Crohn's Disease

Johan van Limbergen and Nikki van der Kruk

Pediatric IBD team

The Children's Abdominal Center (Kinderbuikcentrum) of Amsterdam University Medical Centers (Amsterdam UMC) is a referral center for children with complex abdominal problems.

Here, a multidisciplinary team of Emma Children's Hospital experts bundles its knowledge and expertise to provide the best care for children with gastrointestinal disorders, as well as disorders of the urinary tract and other abdominal organs. A major focus of this Center is the care for children with inflammatory bowel disease (IBD). Dr. de Meij, Dr. Koot and Dr. Van Limbergen are pediatric gastroenterologists and principal investigators at the Emma Children's Hospital/Amsterdam UMC, committed to advancing care for children with Crohn's Disease.

We have a dynamic and multidisciplinary Pediatric IBD team, including pediatric gastroenterologists and surgeons, experienced dietitians, pediatric psychologists, a specialized pediatric IBD nurse, and clinical researchers. Recognizing the complexity of Crohn's Disease and its impact on young patients, our approach integrates medical expertise with holistic care, acknowledging the psychological and nutritional aspects of these conditions. We work closely with the adult IBD team at Amsterdam UMC as well, to facilitate the transition to young adult care.

Dietary Therapies in Crohn's Disease

Crohn's Disease is a chronic inflammatory bowel disease that primarily affects children and adolescents, characterized by inflammation of the digestive tract leading to symptoms such as abdominal pain, diarrhea, weight loss, and fatigue. The incidence of Crohn's Disease is on the rise, posing a significant challenge to healthcare providers worldwide. Our team recognizes the interplay between genetics, the microbiome, and diet in the pathogenesis of Crohn's Disease.

The microbiome, a complex community of microorganisms residing in the gut, plays a pivotal role in the development and progression of Crohn's Disease. Recent research underscores the dynamic relationship between the microbiome and dietary factors. Dietary therapies have emerged as a promising treatment to restore the gut microbiome and offer an integrated approach to managing symptoms and improving the overall well-being of young patients.

Exclusive Enteral Nutrition (EEN) is a recognized and effective treatment for Crohn's Disease included in international guidelines, but the stringent requirement to avoid solid food presents a challenge for patient adherence and reaching long-term remission. Recently, the better tolerated Crohn's Disease Exclusion Diet (CDED) has been a focal point of our research and an increasingly used dietary therapy for children with Crohn's Disease. The CDED is a whole-food dietary approach aimed at reducing inflammation and improving intestinal permeability. By systematically eliminating specific food groups known to trigger inflammation, this diet offers a personalized and sustainable strategy for managing Crohn's Disease in children.

Improving Research and Care for patients with Crohn's Disease

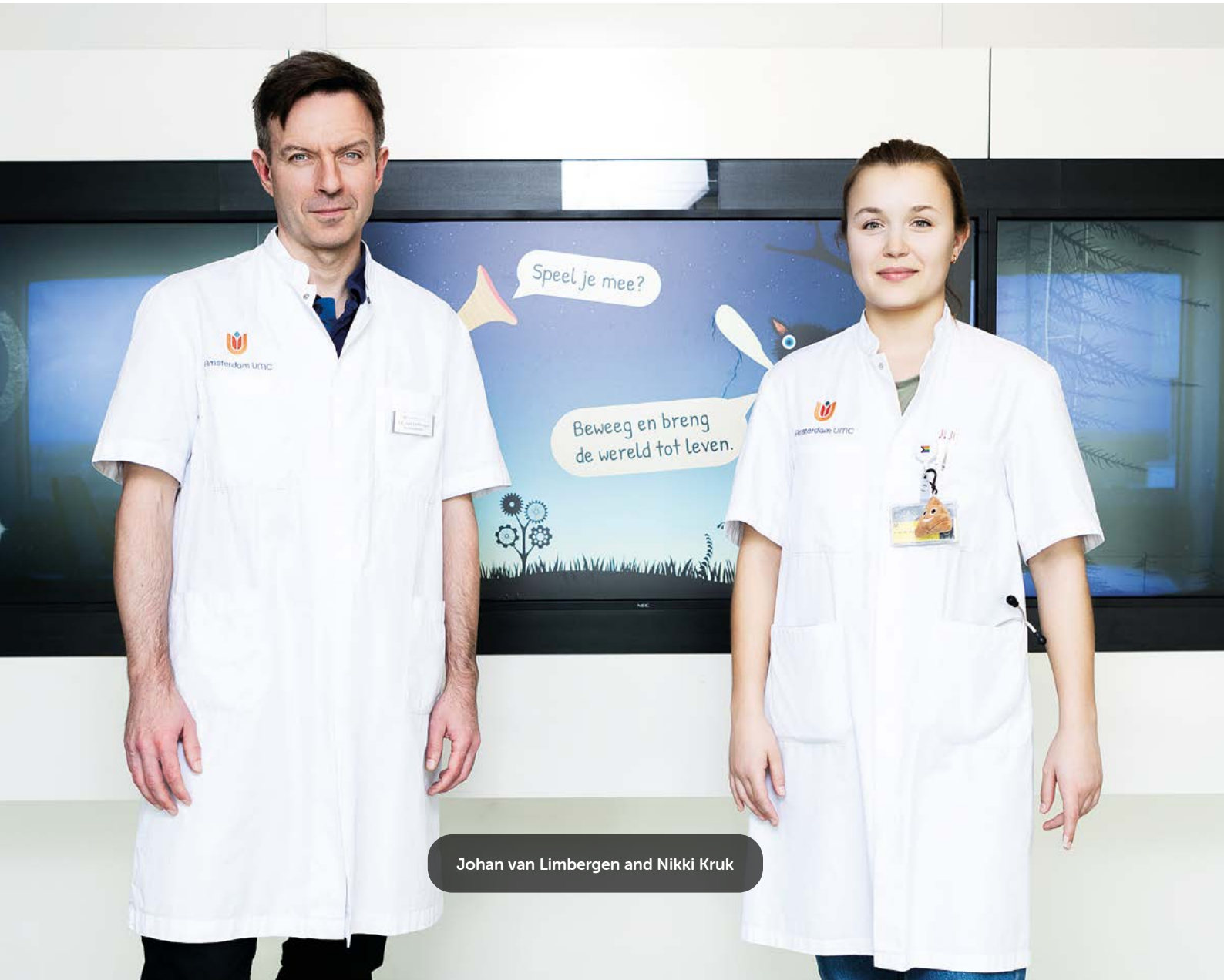
Nikki van der Kruk started her PhD in the IBD team in 2023. She followed up Charlotte Verburgt, who successfully defended her thesis titled "Unravelling the microbiome in Paediatric Crohn's Disease: a journey towards personalised therapy" in June 2023.

Their ongoing research aims to clarify the long-term efficacy and feasibility of the Crohn's Disease Exclusion Diet. To attain this goal, they work closely together with both laboratory researchers at the Tytgat Institute, as well as clinicians in both pediatric and adult gastroenterology.

With a TKI-PPP grant awarded to Johan van Limbergen, they have been developing a study protocol to evaluate the maintenance phase of the Crohn's Disease Exclusion Diet. In this study they will also incorporate measurements of heart rate variability, which could be a promising method for patients to track their stress and recovery to help control their own symptoms better. After medical ethical approval, they plan to start recruiting patients this year.

Also of great importance in our team is the commitment to international collaboration. In 2023 we started with two international multi-center studies, in partnership with esteemed colleagues in Israel and France. One of these studies is observational and aims to unravel the effects of nutritional compounds on inflammatory and metabolic responses of Crohn's Disease patients, to enrich our understanding of the disease progression. While the other is a randomized clinical trial, that will compare the efficacy of CDED to corticosteroids, in inducing endoscopic response. This collaborative effort not only contributes to scientific knowledge but also paves the way for more effective treatment strategies.

Our overarching goal remains to enhance the overall care for patients with Crohn's Disease. Recognizing the multifaceted nature of the condition, our approach extends beyond symptom management to encompass nutritional guidance, psychological support, and comprehensive healthcare strategies. Our multidisciplinary approach, with particular emphasis on dietary therapies, and commitment to international collaboration underscore our dedication to advancing care and improving outcomes for children and adolescents with this chronic disease.



Johan van Limbergen and Nikki Kruk

Bacteriophages to steer the gut microbiome and human disease

Hilde Herrema and Patrick de Jonge

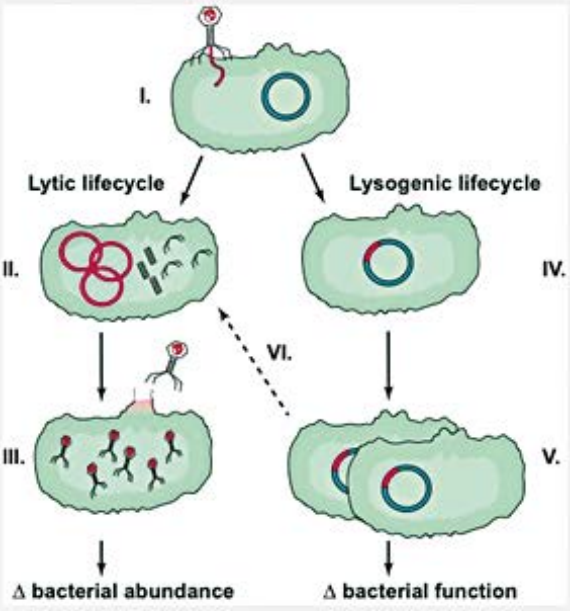
The gut microbiome, a complex community including bacteria, viruses and fungi, aids in human metabolism, digestion and immunomodulation. Gut bacteria can for example convert dietary components into biologically active metabolites able to regulate human metabolism. This makes the gut microbiome an interesting therapeutic target to prevent or improve human disease (e.g., via fecal microbiota transplantation (FMT), biotherapeutics, or diet).

Studies addressing the role of the gut microbiome in human disease typically address its bacterial members. Yet, bacterial community composition and function are shaped by bacteriophages (or phages), which are highly abundant prokaryotic viruses (1:1 tot 1:10 ratio with bacteria) that thereby indirectly affect human metabolism and health.

As prokaryotic viruses, phages exclusively target bacteria. In the gut, phages can control bacterial ecosystems roughly by two modes of action (Box 1). Virulent phages make use of the lytic lifecycle where they kill the host bacterium while producing offspring. They are generally highly specific to a bacterium, thus making them potentially clinically interesting replacements of antibiotics (i.e., phage therapy). Temperate phages make use of the lysogenic lifecycle where the phage DNA is integrated into the host genome. It is then called a prophage, which replicates along with the genome as the bacterial host divides. Importantly, prophages can alter bacterial properties. Together, virulent and temperate phages, via their specific modes of action, alter gut microbiomes and the associated metabolic networks.

The number of publications that associate gut phageomes with human disease (inflammatory bowel diseases, type 2 diabetes, MASLD)the gut phages are often neglected. Results: In this study, we used multiple bioinformatic methods to catalog gut phages from whole-community metagenomic sequencing data of fecal samples collected from both type II diabetes (T2D has expanded in the past years. Individual human gut phages have further been found to mediate diet-induced bacterial lysis, bacterial bile acid metabolism, and gut colonization. Nevertheless, gut phages remain rather elusive entities. Several challenges, including those at the level of identification (e.g., computational challenges) and culturing (e.g., bacterial host identification), as well as lack of human intervention studies using gut phages have thus far stagnated our knowledge on gut phages as regulators of human health.

Our team (funded by AGEM Talent Grant; AUMC PhD Fellowship; DDRF; ZonMW; NWO) addresses exactly these challenges. We recently published a human intervention study where we transplanted healthy donor fecal filtrate (free of bacteria, enriched in phages) to recipients with metabolic syndrome (Nat Commun 2023, PMID: 37699894). Although strong metabolic effects in human



Box 1. Phages, via two distinct lifecycles, can alter gut bacteria and the associated metabolic networks to affect human health. Phages can control gut bacterial communities roughly by two modes of action; the lytic and lysogenic lifecycle. In the lytic lifecycle, the infecting phage (I) produces lots of offspring (II) and kills the bacterial host (III). This lifecycle can affect bacterial community composition. An increase in phage lytic action has been linked to inflammatory bowel disease. In the lysogenic lifecycle, phage DNA is integrated into the bacterial genome (IV). It is then called a prophage, which replicates along with the genome as the bacterial host divides (V). This lifecycle can alter phage and bacterial host diversity. Prophages can be induced upon stimuli including nutrient stress, which leads to extraction from the bacterial host genome and entering of the lytic cycle (VI). Importantly, prophages carry and transfer genes that can alter bacterial properties or function. For example, prophage formation in *Bacteroides vulgatus* was shown to disrupt the ability of the bacterium to metabolize bile acids. In addition, two landmark cases showed that prophage genes enabled bacteria to evade the mammalian immune response or aided in the antitumor response.

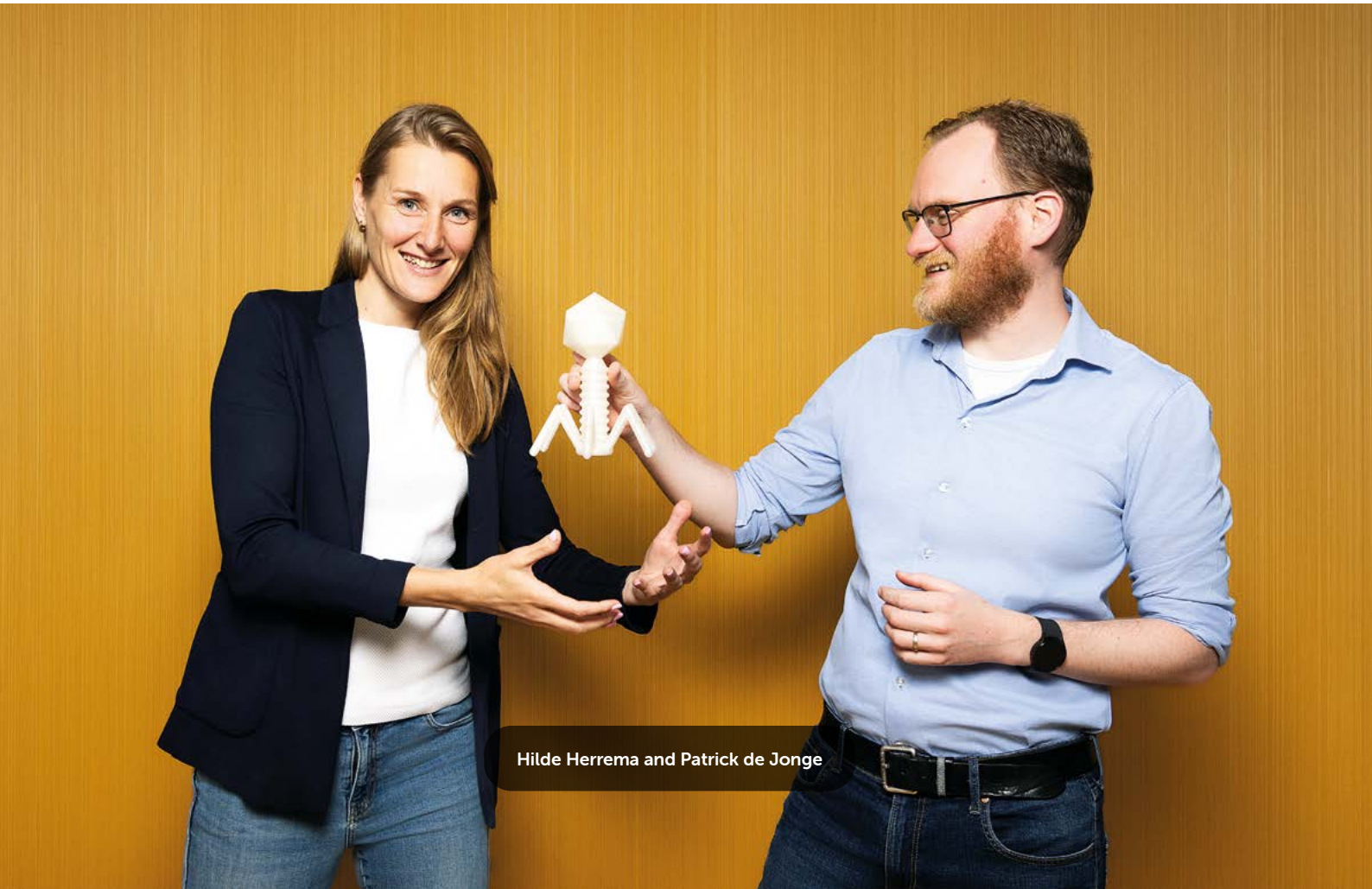
recipients were lacking, the procedure is safe and affects the gut microbiome of recipients. This work provides critical foundation for follow-up studies in better matched donor (phageome) and recipient (bacteriome) pairs.

Here we like to highlight the importance of our computational endeavors to identify phages and to map their behavior in, and effects on, the gut ecosystem – all in context of human disease.

Phage metagenomic studies have several unique challenges. Firstly, unlike bacterial 16s rRNA, phages lack a universal marker gene to simplify study. Not only that, but phage evolution is so rapid and dependent on simultaneous acquisition of whole gene cassettes, that even studying higher taxonomic groupings is difficult. It is because of this until 2022, the accepted phage taxonomy was based on particle shape rather than genome similarity. Consequently, phage studies are limited to analyzing single genomes and thus are difficult to compare to each other. The first phage lineage defined by genome similarity were the *Crassvirales*, which has iteratively been described over the past decade. This has revolutionized human gut phage studies, but it remains the only known higher-order human gut phage lineage.

We recently identified the putative phage family *Ca. Heliusviridae* in a study of gut virome perturbations associated with metabolic syndrome in the Amsterdam HELIUS cohort (Nat Commun 2022, PMID: 35739117). The expansive family was detected in over 90% of 196 study participants and thus is a part of the persistent core of human gut bacteriophage lineages. This study focused on a single cohort; it was hence unknown how widespread these phages are in the general population. Furthermore, their relation to human health beyond metabolic syndrome was yet to be elucidated.

In a comprehensive study of *Ca. Heliusviridae* genomic diversity in over 5000 samples, we showed that this lineage is present in the gut of people from every inhabited continent, and more common there than in other environments. Furthermore, by analyzing fossilized human fecal samples, we determined that these phages started evolving around the time that Homo sapiens first occurs in the fossil record. Their diversity also showed a marked increase, from lowest in ancient peoples and modern hunter-gatherers, via higher diversity among urbanized people, to highest in patients with various diseases (*e.g.*, types 1 and 2 diabetes; inflammatory bowel disease). We thus show the worth of elucidating higher-order structures among gut phage lineages, and provide evidence that some such lineages are directly correlated with our increasingly urbanized lifestyles.



Hilde Herrema and Patrick de Jonge

Postprandial bile acid metabolism in (inherited) metabolic diseases

Maarten Soeters and Soumia Majait

Bile acid team

Our team is a multidisciplinary group within the Academic Center for Gastrointestinal and Endocrinology and Metabolism (AGEM). Dr. Maarten Soeters, an endocrinologist, leads the team. Soumia Majait, a project manager in the hospital pharmacy with a background in nutrition, is pursuing her PhD research on how bile acids respond in patients compared to healthy individuals after a standardized mixed meal. Previous PhD students under Dr. Soeters investigated the role of bile acids in stimulating GLP-1 and insulin secretion, a potentially valuable area for research in obesity and type 2 diabetes mellitus.

The role of bile acids in (inherited) metabolic diseases

Traditionally known for aiding fat digestion, bile acids (BAs) have recently emerged as potential regulators of overall energy balance. A malfunction in bile acid synthesis can lead to lower production and accumulation of toxic intermediates. As example, in Cerebrotendinous Xanthomatosis (CTX), cholestanol and bile alcohols accumulate in extrahepatic tissues, causing atherosclerosis, tendon xanthomas and neurological problems. Fortunately, treatment with chenodeoxycholic acid (CDCA) can restore disrupted bile acid synthesis. CDCA, a primary bile acid, plays a crucial role in regulating its own production through a feedback loop involving the Farnesoid X Receptor (FXR). This receptor, located within the cell nucleus, suppresses CYP27A1, the enzyme controlling the rate-limiting step in bile acid synthesis. Once reabsorbed in the intestine, BAs signal FXR to downregulate their own biosynthesis. Another key player is the Takeda G protein-coupled receptor 5 (TGR5). Research suggests that TGR5 activation by BAs stimulates the release of insulin from the pancreas. Furthermore, TGR5 activation triggers the production of glucagon-like peptide-1 (GLP-1), a major target for type 2 diabetes treatment. Glycochendeoxycholic acid (gDCA), a secondary BA, can activate both FXR and TGR5.

Bile acid as GLP-1 signaling molecules

In the last decades a growing appreciation for the multifaceted roles of BAs in regulating systemic metabolic processes have been witnessed. This modulation is achieved through interactions with specific receptors, including the Farnesoid X receptor (FXR) and the Takeda G protein-coupled receptor 5 (TGR5).

BAs function as endogenous ligands for FXR, which exerts tight control over bile acid synthesis and enterohepatic circulation. This regulatory effect is achieved by modulating the expression of key genes involved in bile acid biosynthesis, transport, conjugation, and detoxification. Beyond FXR activation, BAs also signal through another pathway mediated by TGR5.

TGR5 activation by BAs stimulates the release of glucagon-like peptide-1 (GLP-1) and -2 (GLP-2) from L cells, as well as glucose-dependent insulinotropic polypeptide (GIP) from K cells within the intestine. Both GLP-1 and GIP are known to promote insulin secretion in humans. GLP-1 additionally possesses the ability to decrease food intake and potentially increase energy expenditure. Our department utilizes a comprehensive range of nutritional assessment methods. This includes body composition analysis, energy expenditure measurement, and dietary intake evaluation. We employ advanced tools for each aspect; Bodpod for measuring body composition, Quark indirect calorimetry for measuring energy expenditure and universal eating monitor for measuring food intake.

Furthermore, activation of both FXR and TGR5 has been demonstrated to exert various anti-inflammatory effects on postprandial metabolism through distinct pathways. Intriguingly, postprandial activation of TGR5 by BAs stimulates GLP-1 release, which in turn leads to insulin secretion from the pancreas. This observation highlights GLP-1 stimulation as a promising target for type 2 diabetes therapy. Interestingly, GLP-1 agonists, such as liraglutide and exenatide, are already established treatment options for this condition. A previous study from our group showed that a single dose of gDCA increased GLP-1 levels after a standardized meal. Building on this success, we recently completed a phase 1 clinical trial to assess the safety and metabolic effects of 30-day gDCA treatment in healthy men. However, studying bile acid therapy has its drawbacks.

Challenges of bile acid therapies

One of the challenges we experience and have experienced when setting up the second phase of our study with gDCA, is the fact that the raw material is limitedly available and expensive. It is really challenging for researchers to conduct studies with these expensive BAs. Not only researchers face challenges with bile acid

therapies, but also clinicians and pharmacists. A small spectrum of BAs are registered for specific indications. In case of CDCA as a treatment for CTX, CDCA received an orphan drug status. As a result, CDCA therapy became expensive and health insurance companies were unable to reimburse the costs of CDCA. As an alternative, our hospital pharmacy developed CDCA capsules as a pharmacy preparation for the patient making the therapy accessible for the patients.

A major hurdle in launching our gDCA phase 2 trial is the limited availability and high cost of the raw material. Another hurdle is the side effects of BAs like elevated liver function tests.

Based on our studies it is unlikely that bile acids may be useful to treat metabolic diseases like obesity and type 2 diabetes mellitus type. The strong negative feedback loop within the enterohepatic cycle prevents modulation of individual bile acids.

Soumia Majait

Prevention of surgical site infections

Marja Boermeester, Nathan Bontekoning and Hannah Groenen

Prof. Dr. Marja Boermeester is a Professor of Surgery and Clinical Epidemiologist at the Amsterdam UMC, specialized in surgery of abdominal infections, intestinal failure surgery and complex abdominal wall reconstruction. Her research focusses on complex abdomens such as patients with intestinal fistula and/or infected abdominal meshes. Another important part of her research focuses on the prevention of surgical site infections. She is member of the Amsterdam UMC Research Board, past president of the Surgical Infection Society Europe, and active member of the steering committee of Global Guidelines of Surgical Site Infections at the WHO (World Health Organisation). She has many PhD fellows under her supervision, and several postdocs involved in daily supervision. Currently, her research team is also working on the development of the Dutch guideline for the prevention of surgical site infections and this work is used to update the WHO SSI guidelines.

Prevention of surgical site infections

Surgical site infections (SSI) are the most common nosocomial infections and cause excess morbidity, mortality, and markedly increased healthcare costs. A big proportion is deemed preventable with evidence-based interventions. We investigated the efficacy of different interventions by performing systematic reviews and (network) meta-analyses for the development of the Dutch guideline for the prevention of SSI. The results of four recently performed (network or individual patient data) meta-analyses are interesting to outline.

A network meta-analysis on the efficacy of different preoperative skin antiseptics in the OR on the incidence of SSI has been published in The Lancet Microbe and shows skin preparation using 2.0-2.5% chlorhexidine in alcohol with high certainty of evidence is most effective in any type of surgery, instead of the traditional solution of 0.5% chlorhexidine in alcohol that is widely used in hospitals all over the world. (PhDs Hasti Jalazadeh, Hannah Groenen)

We investigated the use of closed incision Negative Pressure Wound Therapy (ciNPWT) to reduce the risk of SSI in a meta-analysis. This up-to-date meta-analysis shows high certainty evidence that ciNPWT is effective in reducing SSI, and uncertainty is less than in previous meta-analyses. Trial sequential analysis indicated that further trials are unlikely to change the effect estimate. (PhDs Hannah Groenen, Hasti Jalazadeh)

A network meta-analysis on the efficacy of different types of prophylactic intra-operative incisional wound irrigation presents high certainty evidence that antiseptic solutions are effective in reducing SSI. The use of antibiotic wound irrigation should be avoided due to the inferior certainty for its effect, the trivial to no difference in effect compared to antiseptics, and the rapid global antimicrobial resistance to antibiotics. (PhDs Nathan Bontekoning, Hannah Groenen, Hasti Jalazadeh)

We evaluated the effect of the number of door openings in the operating room on the occurrence of SSI in an individual participant data meta-analysis. A mixed-effects logistic regression model indicated that a limitation of the number of door openings to 30 or less per hour or even to ten or less per hour does not result in a reduction of SSI risk, although certainty of evidence is very low. (PhDs Hannah Groenen, Hasti Jalazadeh)

Current projects on surgical site infections

In addition to preventive measures, the timely detection of SSI is crucial for early treatment and minimizing the overall disease burden. In the era of information and technology, the emergence of telemedicine has changed the possibilities for patient follow-up. Particularly with the onset of the COVID-19 pandemic, traditional face-to-face appointments have increasingly transitioned to (video) calls. To ensure the success of this evolving approach, it is essential to deploy robust tools capable of collecting and analysing “Patient Generated Health Data” such as wound photographs and questionnaires.

Addressing this need, Nathan Bontekoning, a PhD candidate under the guidance of Marja Boermeester, is leading the project titled “Recognition of Surgical Site Infections on Wound Photographs with Artificial Intelligence.” The primary objective of this initiative is to develop a sophisticated algorithm capable of recognizing and triaging wound photographs submitted by patients. Similar algorithms are already widely implemented in other medical fields, such as pathology and radiology. The integration of artificial intelligence (AI) in the context of wound photographs holds the promise of enhancing the efficiency and accuracy of SSI diagnosis, ultimately contributing to improved patient outcomes.

Within the same study, the Dutch version of the Bluebelle Wound Healing Questionnaire is being validated. This patient centred questionnaire, translated from the UK version, accurately determines the presence of an SSI.

The ultimate goal is to combine both the Bluebelle questionnaire and the AI algorithm to create a reliable tool for patients to report potential complications and receive advice on whether to consult a physician.

Nathan Bontekoning and Hannah Groenen

HPB research

Rogier Voermans and Anouk Overdevest on behalf of the HPB research team.

The HPB research group focusses on improving outcome for patients with hepatico-pancreatico-biliary (HPB) diseases. This is mainly achieved by conducting large trials in multidisciplinary, multicenter, strong collaboration networks in the Netherlands and abroad. For (pre) malignant biliary diseases translational research is performed as well. The main focus of the research is on pancreatitis, benign biliary diseases, (pre)malignant biliary diseases, and advanced/innovative endoscopy. One example of a research line concerns cholangitis.

Cholangitis

A bile duct infection (or 'acute cholangitis') generally occurs due to an outflow obstruction in the bile ducts, in combination with the presence of bacteria. The therapeutic approach of acute cholangitis involves two primary actions: (1) removing the biliary obstruction in order to achieve source control and (2) administering antibiotic therapy. Gallstones ('choledocholithiasis') is the most prevalent cause of biliary obstruction, with less common sources including bile duct or pancreatic cancer, and chronic progressive disorders such as 'primary sclerosing cholangitis'. The obstruction can be resolved by performing an endoscopic retrograde cholangiopancreatography (ERCP). During ERCP, gallstones can be removed or a stent can be placed to restore normal bile flow. Given that acute cholangitis is a bacterial infection, an additional course of antibiotics is an essential part of the treatment strategy.

Optimizing treatment of cholangitis

Anouk Overdevest started her PhD in January of 2023. Her line of research focuses on optimizing the treatment strategy of acute cholangitis. One of the major issues in treating cholangitis is that there are no randomized studies to guide the exact duration of antibiotic therapy. National and international guidelines – mostly based on low quality evidence – are contradictory, suggesting antibiotic courses from 1 - 3 days to 4 – 7 days. Our research team conducted a retrospective study that showed that, although a short course of antibiotics seems safe, more than half of the patients received a more extended duration than recommended by the national SWAB guideline.

Evidence has been accumulating that many other bacterial infections, including abdominal infections, can be treated with a shorter course of antibiotics than previously assumed. Recent RCTs have showed that uncomplicated intra-abdominal infections, such as acute cholecystitis or appendicitis, can be adequately treated without post-operative antibiotics as long as the source of the infection is adequately treated by surgical intervention.

Motivated by these findings, our goal is to bring resolution to this ongoing debate about the optimal duration of antibiotic therapy by conducting a well-designed RCT, known as the COBRA trial. The objective of this study is to show that very short-course antibiotics (1 day) is equally safe and effective when compared to a longer course of antibiotics which is recommended by the international Tokyo guidelines (4 – 7 days). More than 30 hospitals across the country are participating in this study, which is both a challenging and enjoyable collaboration.

Another line of research focuses on a more specific group of patients who suffer from cholangitis. Since Amsterdam UMC is considered an expert center for surgical treatment of hepatobiliary and pancreatic diseases, many patients undergo major operations that require a new biliary-enteric anastomosis, a so-called hepaticojejunostomy (HJ). Most surgical procedures requiring an HJ are pancreatoduodenectomies or liver resections. Indications for these surgeries can be either benign disease, such as bile duct injuries or biliary strictures that cannot be treated adequately in an endoscopic way, as well as malignant disease. These operations are considered high-risk procedures with a major complication rate of around 30%.

The most common infectious complication is post-operative cholangitis. As previously mentioned, biliary obstruction plays a critical role in the development of cholangitis. This is often caused by a problem at the site of the HJ anastomosis, by either tumor recurrence or a benign bile flow obstruction. In these cases, the most obvious solution is to restore bile flow by performing a re-operation or (endoscopic) dilatation of the HJ. However, some patients who suffer from post-operative cholangitis do not show any signs of HJ stenosis. Non-stenotic cholangitis (NSC) is relatively rare, but poses major clinical challenges for treating physicians. Because no clear substrate for treatment is available, this often leads to a high recurrence rate and to the use of long-term antibiotics. Our research team carried out the first retrospective study focusing on patients who suffer from recurrent non-stenotic cholangitis and found a cumulative incidence of 4.4%. Furthermore, we found that these patients with NSC suffer from a median of 7 episodes per patient which is associated with a high disease

burden for these patients. Due to a lack of scientific data and consensus among medical specialists, there is no standardized treatment strategy available. Our research team developed a flowchart for diagnostic and therapeutic management for these patients that will be put into clinical practice very soon. After this, we will prospectively collect data across the Netherlands.

Anouk Overdevest and Rogier Voermans

Endocrine Laboratory

Annemieke Heijboer and Heleen Jansen

Impact of Endocrine Laboratory Medicine

The Amsterdam UMC Endocrine Laboratory is one of the five laboratories of the department of Laboratory Medicine. Prof. Dr. Annemieke Heijboer, clinical chemist-endocrinologist, is head of the Endocrine Laboratory since the merge of the Endocrine Laboratory of VUmc and the Laboratory of Endocrinology of the AMC in 2018. From 2015 until 2019 she was the president of the Dutch Society for Endocrinology and now she is a member of the Bone committee of the International Federation of Clinical Chemistry and chair of the Endocrine committee of the Dutch Society for Clinical Chemistry. Her research focusses on Endocrine Laboratory Medicine, with a special interest in steroid and thyroid hormones. This research includes all aspects of biomarkers, from *pre-analysis* (Is there a need for fasted blood withdrawal? Are dried blood spots, which can be sampled at home, an alternative for a venipuncture?) and *analysis* (development of reliable methods to measure hormones, accuracy of methods in specific patient groups) to post-analysis (establishment of reference intervals and cut-off values). She also works on the search for new biomarkers (for instance for idiopathic hirsutism) and the applicability of these biomarkers in the diagnostic setting. All studies aim to have impact on patient care by giving physicians better tools to improve diagnosis or follow up of their patients. The merge of the AMC and VUmc Endocrine Laboratories made it possible to have different specialists working more closely together and has given a boost to the research performed in the Endocrine Laboratory. This led to more collaborations with a diversity of national and international experts and more multidisciplinary studies, with social impact. The Endocrine Laboratory works for instance on health economy aspects, artificial intelligence and patient perspectives and aims to have impact on topics such as sustainability and diversity & inclusion.

Thyroid hormones measurements: implications for patient care

Heleen Jansen is a highly talented PhD student, working in the Endocrine Laboratory of Amsterdam UMC. She started in 2021 after her medicine study at the VU University and after gaining work experience as resident not in training (ANIOS) at the department of internal medicine of Noordwest Ziekenhuisgroep (NWZ) Alkmaar. She plans to finish her PhD thesis in the year 2024. Her studies about pitfalls and improvement in laboratory measurements of thyroid hormones include many of the topics mentioned above. She was able to show that most immunoassays that are currently used in clinical laboratories are not able to measure free T4 accurately in samples from pregnant women and from persons undergoing hemodialysis. This is highly relevant information for clinicians and laboratory specialists as almost everyone assumes that these methods are very accurate. In addition, she was involved in the development of several new methods, i.e. the reference method for free T4 in collaboration with Radboud UMC and a method for reverse T3, T3 and T4, including method comparisons with several international laboratories. She set up a method comparison in our Endocrine Laboratory to evaluate a recently developed immunoassay measuring TSH receptor antibodies. Moreover, she performed two reference interval studies, crucial for the right clinical interpretation of thyroid hormone measurements. One of these studies, a Dutch consortium study with thirteen different clinical laboratories, led by the Amsterdam UMC, will further stimulate the national and international debate about the implementation of age-dependent reference intervals for TSH and free T4 in the elderly. In addition to these rather practical studies with direct implications for patient care, Heleen also searched for new biomarkers to better describe the thyroid hormone status than the currently used TSH, free T4 and free T3 measurements. It is known that despite having these thyroid hormone concentrations within the reference interval, patients can still have symptoms. This might be due to the fact that these serum markers not necessarily reflect the tissue thyroid hormone status. Literature studies were performed to look for additional biomarkers and some of these additional biomarkers in combination with artificial intelligence (a machine learning model) were successfully used to improve the neonatal screening for congenital hypothyroidism. Moreover, Heleen started the prospective ANTICIPATE study to improve the determination of the thyroid hormone status in patients using thyroid hormone supplementation (levothyroxine) since she confirmed in a previous study that free T4 can show concentrations above the upper limit of the reference interval in levothyroxine treated patients without having an abnormal thyroid function. Last but not least, she studied the patient and clinician perspectives on the GREAT+ score through a survey among patients with Graves' Disease. All these studies, directly or indirectly, improve care for patients who suffer or are suspected to suffer from thyroid diseases. Highlights achieved by these and also the other studies performed within the Endocrine Laboratory are published on the Endocrine Laboratory LinkedIn page.

Annemieke Heijboer and Heleen Jansen

Targeting the underlying causes of aging

Georges Janssens and Weisha Li

What causes aging?

Researching the biology of aging is paramount for addressing the challenges posed by an increasingly aging world population. From a global perspective, the study of aging provides critical insights into the intricate processes influencing healthspan and lifespan, with far-reaching implications for healthcare, societal structures, and economic systems. This research serves as the cornerstone for understanding age-related diseases, identifying potential interventions, and ultimately enhancing the quality of life in later years.

Systems Biology of Aging Team.

The team of Dr. Georges E. Janssens is embedded in the Laboratory Genetic Metabolic Diseases at the Amsterdam University Medical Center, location AMC, and is part of the Amsterdam Gastroenterology Endocrinology and Metabolism Institute. Three key research avenues drive the team's investigation into aging: (1) understanding the mechanisms of aging, (2) developing Biological Aging (BioAge) measures, and (3) performing Geroprotector drug discovery, i.e. to identify drugs that 'protect' the gerontological phase of life.

The team's work on mechanisms of aging delves into the molecular and cellular processes that govern how cells and tissues change over time. The team is agnostic towards any particular theory of aging and rather takes a systems-biology perspective, with the idea that only by measuring many different levels of biology will it be understood what happens during aging. This research approach offers diverse insights to be made, from metabolism to protein translation, from cardiac function to dementia. BioAge measures represent another critical focus of the team, providing quantifiable metrics to assess an individual's biological age. Here the team employs various approaches to quantify aging, ranging from plasma metabolomics to blood biochemistry measures to even wearable device movement patterns. This avenue involves the development and refinement of accurate measures that reflect how an individual's biology aligns with chronological age. Such measures enable early identification of those at higher risk for age-related diseases, facilitating targeted interventions for personalized and preventative healthcare. Indeed, the ultimate goal of researching and tracking the aging process is to intervene in it, to promote health during aging. In this regard, to identify candidate small molecules capable of extending healthspan, the team employs innovative approaches that integrate machine learning and in silico computational drug screening methodologies leveraging a vast database of cellular signatures from 20,000 small molecules.

Low Dose Naltrexone (LDN).

Within the realm of drug discovery, the team has identified Low-Dose Naltrexone (LDN) as a candidate geroprotector through computational drug screening. Led by PhD student Weisha Li, the research on LDN explores its effects on health span and lifespan using the model organism Caenorhabditis elegans. Weisha's research has revealed that low (but not high) doses of LDN extend both health span and lifespan in these worms, showcasing its potential as a lifespan-extending agent. Weisha investigation into LDN goes beyond mere observation, delving into the mechanistic intricacies that underlie its geroprotective effects. The study has identified the critical involvement of the SKN-1/NRF2 signaling pathway, a key regulatory mechanism associated with oxidative stress response and innate immunity gene expression. This discovery not only sheds light on the specific molecular targets influenced by LDN but also provides a nuanced understanding of how LDN may exert its beneficial effects on aging-related processes.

The central role of the SKN-1/NRF2 pathway in LDN's impact on oxidative stress response and innate immunity gene expression reveals a potential mechanism for promoting healthy aging. By activating this pathway, LDN appears to enhance the organism's ability to cope with oxidative stress and bolster its innate immune defenses, both critical aspects of maintaining overall health span. With NRF2 activators demonstrated to have health span-benefiting effects in mice by other labs, Weisha's work identifying LDN as a geroprotector offers an especially high potential avenue for translation to practical application. This is due to LDN's established low side effects profile in humans, paired with Weisha's demonstrated geroprotective efficacy in *C. elegans*.

The work of Weisha on LDN does not stand on its own. Over the last years, LDN has emerged as a therapeutic agent with a multitude of off-label uses, extending well beyond its initial FDA-approved indications for alcohol and opioid dependence. Studies and clinical observations have suggested its efficacy as an adjunct treatment for various conditions, including cancers, autoimmune diseases, chronic pain, and mental health issues. LDN's

immunomodulating properties have been explored for their ability to mitigate oncogenic and inflammatory autoimmune processes. Additionally, its impact on neurotransmitter systems has led to investigations into its potential for alleviating symptoms in certain mental health disorders. The versatility of LDN in addressing such a wide spectrum of medical conditions highlights its potential as a promising candidate for further exploration and underscores the need for rigorous research to elucidate its mechanisms of action and optimize its application in various therapeutic contexts. Thanks to Weisha's extensive research on LDN in *C. elegans*, 'geroprotection' has now been added to the list of translational follow up possible for LDN.

Weisha Li and Georges Janssens

Best Publication 2023

In 2024, AGEM again organized the Best Publication battle. For this, all AGEM principal investigators (PIs) had the opportunity to nominate publications of their best researcher, PhD student or postdoc, that published as first author in a top journal in 2023. Out of these nominees, members of the AGEM Research Board selected a top 3. These selected candidates were offered a pitch workshop and, with the skills learned, Heleen Jansen, Katy van Galen en Sebastian Hendrix pitched their publication during the AGEM award ceremony on May 23rd, 2024. After this so-called "AGEM Best Publication 2023 Battle", the attendants of the award ceremony voted for their ultimate favorite. The author of the publication with the most votes was named winner of the AGEM Best Publication 2023.

Please meet the nominees for the AGEM Best Publication 2023...

Katy van Galen

Katy van Galen was nominated by Mireille Serlie for her article published in Nature Metabolism: "*Brain responses to nutrients are severely impaired and not reversed by weight loss in humans with obesity: a randomized crossover study*". Nat Metab. 2023 Jun;5(6):1059-1072

The motivation of Mireille Serlie for the nomination was: "The paper is the first to show that, in people with obesity, brain nutrient sensing and nutrient-induced striatal dopamine release is altered. These findings might explain why people with obesity eat beyond caloric need."

Heleen Jansen

Heleen Jansen was nominated by Anita Boelen and Annemieke Heijboer for her article published in the European Thyroid Journal: *"Optimizing the Dutch newborn screening for congenital hypothyroidism by incorporating amino acids and acylcarnitines in a machine learning-based model"*.
Eur Thyroid J. 2023 Nov 3;12(6):e230141.

The motivation of Anita Boelen and Annemieke Heijboer for the nomination was: "For the aforementioned article, Heleen has described a machine learning model that can significantly improve screening for congenital hypothyroidism. Heleen set up this research herself and has since presented it at national and international meetings. Moreover, the responses from the committees involved in neonatal screening have been so enthusiastic that permission has been granted for follow-up research, and there is a desire to add this model to the national neonatal screening program".

Sebastian Hendrix

Sebastian Hendrix was nominated by Noam Zelcer for his article published in Nature Communications: "*Hepatic SREBP signaling requires SPRING to govern systemic lipid metabolism in mice and humans"*.
Nat Commun. 2023 Aug 25;14(1):5181.

The motivation of Noam Zelcer for the nomination was: "In this paper Sebastian demonstrated for the first time that an unknown gene that we identified, SPRING (C12ORF49), is a key determinant of the SREBP pathway in vivo and as such plays a critical role in controlling hepatic cholesterol and fatty acid synthesis. Beyond being the first new gene in 2 decades to be recognized as a component of the core machinery that controls SREBP activation this work also highlights potential targeting of SPRING in MASLD and CVD."

And the winner of the AGEM Best Publication 2023 is...

Sebastian Hendrix

My name is Sebastian Hendrix and I am a PhD candidate in the group of Prof. Noam Zelcer within the Department of Medical Biochemistry. Already while studying Biochemistry and Molecular Biology in Graz, Austria, I became intrigued with the intricacies of the human metabolism. It fascinates me, how the human body can sustain its complex machinery with an input of only ~200-300 grams of carbohydrates per day. I am very interested in advancing our understanding of the metabolic processes underlying that machinery, and how they are changed under pathological conditions. That is why I decided to join Noam's lab, which gave me the opportunity to pursue those interests. Our group focuses on investigating the molecular regulation of lipid metabolism in the context of cardio-metabolic diseases. More specifically, my work evolves around SPRING, a novel regulator of lipid metabolism that was identified in the group in 2020. In the course of my PhD, I focused on unraveling the mechanism by which SPRING is modulating lipid metabolism, and on the physiological implications of SPRING in mouse models.

Zelcer Group

SPRING-dependent regulation of hepatic SREBP signaling governs systemic lipid metabolism in mice and humans

The sterol regulatory element binding proteins (SREBPs) are transcription factors that govern cholesterol and fatty acid metabolism. Owing to their central role in controlling lipid and lipoprotein metabolism their activity is tightly coordinated. Accordingly, dysregulation of the SREBP pathway is associated with development of pathologies like dyslipidemia and non-alcoholic fatty liver disease.

Using a suite of genome-wide genetic screens we have recently identified SPRING (SREBF Pathway Regulator In Golgi 1; formerly C12ORF49) as a novel post-transcriptional regulator of SREBP activation in vitro. In previous work, we demonstrated that constitutive ablation of Spring in mice is embryonically lethal. Here we show that inducible global deletion of Spring is also fatal, and therefore to interrogate the physiological role of SPRING in controlling hepatic lipid metabolism we developed liver-specific Spring knockout mice (LKO). Liver transcriptomics and proteomics analysis revealed severely attenuated SREBP signaling in livers and in hepatocytes of LKO mice, which was associated with marked effects on both plasma and hepatic lipid levels. In plasma, total cholesterol levels were dramatically reduced in both male and female LKO mice, apparent in both the LDL and HDL fractions, while triglyceride levels remained largely unaffected. In liver, loss of Spring diminished cholesterol and triglyceride biosynthesis resulting in decreased hepatic cholesterol and triglyceride content. This coincided with reduced secretion of VLDL into the circulation. Consistent with diminished hepatic de novo lipogenesis, LKO mice were protected from developing hepatosteatosis when challenged with a fructose-rich diet.

Supporting the significance of our findings in mice, we identified common and rare SPRING genetic variants that are strongly associated with circulating HDL-c and ApoA1 levels in humans.

Collectively, our study positions SPRING as a central regulator of hepatic SREBP signaling, and consequently of systemic lipid metabolism in mice and humans.

Grants 2023

In 2023, AGEM awarded four types of grants. Like previous years AGEM awarded the AGEM talent development grant for exceptionally talented researchers who are in the first 5 years after obtaining a PhD-degree and want to start their own research line (VENI-like-profile) or who want to further develop their own research line (VIDI-profile, max 8 years after PhD graduation), the AGEM innovation grant for innovative ideas beneficial to the AGEM research institute as a whole, the AGEM international student fellowship for (bio-)medical students (in their MSc-program or just graduated) to participate in a research internship for a 6-12 months at an international top institute, and the AGEM contribution printing costs of theses for AGEM PhD candidates.

The AGEM talent development grant 2023 (€50.000)

Inez Verpalen (VENI-like-profile)

Automated MRI-based radiomics to predict high-grade dysplasia and cancer in patients with Intraductal Papillary Mucinous Neoplasms of the Pancreas (PRIMA-2).

Inez Verpalen

I am a resident in Radiology with a special interest in hepato-pancreato-biliary (HPB) imaging. I have previously completed a PhD in abdominal radiology. After obtaining my PhD I have started my own research group that focuses on the use of artificial intelligence in abdominal imaging. The goal of my research is to use AI to detect lesions, to characterize them and to determine further treatment.

The AGEM talent development grant allows me…

.. to search for an imaging biomarker to distinguish pancreatic cystic neoplasms (IPMN) that are at low-risk (low-grade dysplasia) from those that are at high-risk (high-grade dysplasia) of developing invasive cancer. Intraductal papillary mucinous neoplasms (IPMN) are common cystic neoplasms of the pancreatic gland and they are considered a benign entity with malignant potential. However, this progression to malignancy is only seen in a very small percentage of these cysts, and their appropriate management represents a growing clinical challenge. Unfortunately, current techniques fail to accurately discriminate between low-risk and high-risk IPMN. MRI-based radiomics analysis has shown potential in differentiating benign from malignant IPMN. Therefore, we aim to investigate an automated MRI-based radiomics approach to differentiate between low-grade dysplasia and high-grade dysplasia IPMN. The model will be developed and externally validated based on surgical IPMN patient cohorts (only patients who underwent pancreatic resection). These models can aid the surgeon in optimal treatment selection for patients with IPMN. Patients with high-risk IPMN would be sent for resection, whereas patients with low-risk cystic lesions would be spared an invasive procedure.

Inez Verpalen

Arwen Gao (VENI-like-profile)

Modulation of complex lipids to prevent aging

Arwen Gao

I am specialized as a biomedical scientist and have extensive experience in metabolism, aging, and genetics in C. elegans. I was awarded an AMC PhD scholarship in 2014 to pursue my PhD thesis, focusing on the metabolic control of aging in C. elegans, and I earned my PhD degree in the fall of 2018 at the University of Amsterdam in the Netherlands. I continued my research on mitochondrial stress response and its role in metabolism and aging, under the supervision of prof. Johan Auwerx (EPFL, Switzerland) and supported by a post-doctoral fellowship (2019 Accelerator price winner). During the 3.5-year postdoc training, I initiated several projects focused on the role of lysosomes and their functions in mitochondrial stress responses and longevity. In the summer of 2022, I moved back to the Netherlands supported by the Amsterdam UMC Postdoc Career Bridging Grant and Marie Curie fellowship (HORIZON-MSCA-2022-PF-EF) and am currently an Assistant Professor at the Amsterdam UMC - Location AMC. My research focuses on lysosomes, lipids, aging, and translational projects that can benefit patients with lysosome disorders.

The AGEM talent development grant allows me…

… to study the role of complex lipids (e.g. phospholipid BMPs) in the regulation of the aging process. I hypothesize that phospholipid classes beyond BMP change in abundance with age in a detrimental manner, and can be reversed by modifying lipid metabolic pathways to ultimately promote longevity. I will use mouse lipid data profiles, worm C. elegans, and apply a combination of molecular, biochemical, and phenotypic experiments with a focus on lipids and aging. The proposed experiments will lead to a better understanding of conserved complex lipid changes and the role of Pla2g15 in the BMP synthesis cascade relevant to health and disease during aging. This research will pave the way not only for redefining the important role of complex lipids in aging regulation but also for providing new targets for tracing age-related changes (altered complex lipid levels, such as BMPs). I believe that with the support of this grant, my proposed research will strongly impact the conventional perception of complex lipids in the field of aging studies.

Arwen Gao

The AGEM innovation grant 2023 (€25.000)

Koen Dreijerink

An integrative epigenetic approach to identify novel markers of hormone treatment response

Koen Dreijerink

Koen Dreijerink is an endocrinologist who was trained as a physician-scientist and is interested in functional epigenetic aspects of endocrine tumor development and hormone action. He works in the Amsterdam Center for Endocrine and Neuroendocrine Tumors (ACcENT) and the Center of Expertise on Gender Dysphoria (KZcG).

The AGEM innovation grant allows us…

With this grant we have set up a protocol called CUT&RUN in the endocrinology laboratory, which enables analysis of genome-wide histone modification presence and transcription factor occupancy in cells and tissues. CUT&RUN is a micrococcal nuclease-based method that can be carried out in a single day and because of low background levels requires limited amounts of cells and sequence capacity. We will use CUT&RUN in an integrative manner with RNAseq to identify markers of hormone response, as a first step in PBMCs of patients on thyroid hormone withdrawal for thyroid cancer treatment. Future steps will involve expanding the approach to other hormone receptors and tissue types, as well as making CUT&RUN available to the broader AGEM research community.


Koen Dreijerink

Nanne de Boer, Evelien Dekker, Sofie Bosch and Roza Opperman

Non-invasive faecal amino acid profiles, volatile organic compounds and FIT for surveillance after piecemeal polypectomy: toward less unneeded colonoscopies

Nanne de Boer

Nanne de Boer is associate professor and has been a gastroenterologist at Amsterdam UMC since 2011, specializing in inflammatory bowel diseases (IBD). In addition to this ongoing research line on repurposing and optimizing IBD drug therapies, he also leads research on faecal non-invasive biomarkers for detecting and monitoring IBD, as well as colorectal polyps/dysplasia and cancer. Specifically, volatile organic compounds, the microbiome, and amino acids are studied in stool samples. Currently, he serves as the co-director of the AGEM research institute.

Evelien Dekker

Evelien Dekker is professor of Gastrointestinal Oncology, particularly focusing on screening and diagnosis of colorectal carcinoma both in average risk populations and high-risk populations such as hereditary polyposis and cancer syndrome patients. She has been one of the frontrunners for the Dutch national CRC screening program, and is still involved in the program's evaluation and quality assurance. She combines her clinical work as a gastroenterologist with clinical and translational research, leading the CRC research group at AUMC since 2005.

Sofie Bosch

Sofie Bosch is a postdoctoral research fellow and gastroenterologist in training. In 2021, she successfully defended her PhD thesis in which she focused on the evaluation of new non-invasive biomarkers for IBD and CRC. Sofie has keen interest in translational research, focusing on omics strategies and machine learning for the early detection and effective monitoring of gastrointestinal disorders. She integrates this interest into her scientific work alongside her clinical work and has also been closely involved as a co-promoter since April 2022.

Roza Opperman

Roza Opperman studied medicine at Amsterdam UMC and began as a PhD candidate in the CRC research group in April 2022. She is currently working on non-invasive biomarkers for colorectal neoplasia detection and surveillance. She is particularly interested in faecal amino acids as a new biomarker. In addition to studying amino acid profiles, she is also engaged in researching volatile organic compounds, the microbiome, bacterial proteome, and proteases to explore their roles and biomarker potential in colorectal neoplasia.

Sofie Bosch and Roza Opperman

The AGEM innovation grant allows us…

… to study new potential non-invasive biomarkers for the surveillance of patients receiving piecemeal endoscopic mucosal resection (pEMR) of colorectal dysplastic lesions. These non-invasive biomarkers aim to guide the optimal timing for surveillance colonoscopy. This can lead to a decrease in burdensome, costly, and unnecessary surveillance colonoscopies, reducing pressure on colonoscopy capacity and potentially lowering healthcare costs. Faecal immunochemical testing (FIT) has already showed to be patient friendly, high-trough output and feasible for screening, however, its potential for surveillance after pEMR remains to be investigated. Recently, faecal amino acids and volatile organic compounds (VOCs) were shown to hold great potential as biomarkers for follow-up of colorectal adenomas (after removal) and therefore, it could also be of value for surveillance after pEMR. Different techniques as gas chromatography-ion mobility spectrometry (GC-IMS), liquid chromatography – tandem mass spectrometry (LC-MS/MS) and the FIT will be used. This project and study design can lead to many more (translational) research in the field of alternative surveillance approaches for colorectal neoplasia. Finally, the techniques used and developed in this project, along with the samples we collect and store in the biobank, can also be used for other studies within the AGEM research field.

Eveline Bruinstroop, Anita Boelen and Annemieke Heijboer

Uncovering the unknown pool of thyroid hormone by LC-MS/MS?

Eveline Bruinstroop

Eveline Bruinstroop is an Internist – Endocrinologist specialized in thyroid and metabolic liver disease at the Department of Endocrinology and Metabolism of the Amsterdam UMC. Her research focuses on thyroid hormone regulation of liver metabolism and is performed at the Laboratory of Endocrinology together with Professor Anita Boelen and the clinical department of Endocrinology. Additionally, she co-leads a work package in a recent NWA subsidy investigating the metabolic effects of menopause in a liver-on-a-chip model to complement clinical data. As a consecutive member of the grant committee for Fulbright she enjoys contributing to the career of more junior scientists.

Anita Boelen

Anita Boelen, PhD, is a Professor of Thyroid Hormone Metabolism, in particular molecular and diagnostic aspects, in the Endocrine Laboratory at the Amsterdam University Medical Center, University of Amsterdam. She is a basic scientist with a research focus on thyroid hormone metabolism in innate immune cells and on mechanisms involved in congenital central hypothyroidism and also head of the regional Dutch Neonatal Screening program at the Endocrine Laboratory and responsible for the measurements in heel prick blood of neonates born in the region Noord Holland and Flevoland. Currently, she serves as the co-director of the AGEM research institute.

Annemieke Heijboer

Annemieke Heijboer is a Professor in Endocrine Laboratory Medicine and head of the Endocrine Laboratory of the Amsterdam UMC, the largest endocrinology laboratory in the Netherlands. She has made a strong profile at the intersection of clinical chemistry and endocrinology by developing new analyzes for the determination of hormones. This led to winning the “Young Investigators award for Clinical Chemistry” in 2014 and, based on many scientific successes, she was eventually asked to become a board member and chairman of the Dutch Endocrine Society from 2012 till 2019.

The AGEM innovation grant allows us…

… to establish a reliable LC-MS/MS method for the conjugated forms of thyroid hormones (TH) in serum, tissue and feces. The actual TH tissue concentrations are determined by the activation or inactivation of TH via deodination, sulfation and glucuronidation. The sulfated and glucoronidated forms of TH are secreted via the gut but can be re-absorbed and de-conjugated in the intestine and liver. It is tempting to speculate that this might be a reservoir of TH if needed. The conjugated forms of thyroid hormone are currently not measured due to the lack of reliable assays. By developing this method and thereby able to measure the conjugated forms in various matrices it is possible to uncover the now unknown pool of TH in the body which may have an important clinical relevance for patients with hypothyroidism. The development of a method to measure hormones in various matrices is an innovation useful for others within the AGEM institute and beyond. This grant also supports the ongoing collaborations between different departments (Endocrinology, Endocrine Laboratory, Vascular Medicine).

Eveline Bruinstroop, Anita Boelen and Annemieke Heijboer

Mireille Serlie, Gerd Bouma, Natascha van Rijssen, Airin Simon and Nicolette Wierdsma

The effect of oral fructose on functional enterocyte mass in patients with intestinal failure; a feasibility pilot study

Mireille Serlie

Being a physician scientist puts me at the crossroads of bed and bench. My research questions are focused on relevant patient problems and include topics in the fields of obesity, insulin resistance, brain mechanisms of food intake, and nutrition. Clinically, I am also involved in the treatment of intestinal failure patients. Patients that are dependent on parenteral nutrition have a lower quality of life and finding novel solutions to reduce their disease and treatment burden is one of the major goals of the research program of the TPN and intestinal failure expert center.

Gerd Bouma

Gerd Bouma studied medicine and medical biology at the Vrije Universiteit Amsterdam where he obtained his PhD on the immunogenetics of chronic inflammatory bowel disease. After a postdoctoral fellowship in the field of mucosal immunology at the National Institutes of Health in the United States, he specialized in gastroenterology and has been working as a staff member of the department of gastroenterologist at the VU Medical Center. In 2015, he was appointed professor of inflammatory bowel disease. He has a special interest in the diagnosis and treatment of disorders of the small intestine.

Natascha van Rijssen

Natascha van Rijssen is dietitian with a Master's degree in Health sciences and PhD candidate at the TPN and intestinal failure expert center. "I work with the patients and the problems they deal with every day. Finding a solution for nutritional and physical problems together with the patient is a big part of my job and it is my motivation to do research in this population: study potential solutions to reduce the disease and treatment burden and implement these into daily practice".

Airin Simon

Airin Simon did her PhD at the clinical diabetology research group of the Amsterdam UMC, focusing on optimizing the treatment for patients with type 2 diabetes. She currently works as a internist-endocrinologist at the TPN and intestinal failure expert center. "As a doctor being confronted with struggles of patients that are dependent on parenteral nutrition on a daily basis I am highly motivated to perform research aiming at improving their quality of life".

Nicolette Wierdsma

Nicolette Wierdsma is a dietitian-researcher working in the Department of Dietetics at Amsterdam UMC. As a dietitian, she works for the department of gastrointestinal and liver diseases and is specialized in diagnosis and treatment of patients with intestinal insufficiency. Her research focuses on role of nutrition in disease (a.o. malabsorption, GI oncology, intestinal failure, IBD and ICU). Together with Gerd Bouma she treats patients with complex nutritional problems in MDL diseases and supervises physician assistants within the internship Nutrition (part of the MDL physician training). She participated in various (inter)national guidelines and committees (ESPEN, ECCO) and was co-founder and chairman of the dietician network MDL. Together with Hinke Kruizenga she is initiator and author of Pocketbook of Dietetics, and co-author of both the Dietetic Pockets Guides.

Airin Simon and Natascha van Rijssen

The AGEM innovation grant allows us…

… to explore a potential novel treatment to increase intestinal absorptive capacity in patients with intestinal failure that are dependent on parenteral nutrition. We will assess whether enteral fructose increases enterocyte function and mass in a pilot study. If the administration of fructose is feasible, we will apply for funding to perform a randomized crossover trial. If successful, fructose treatment might also be applied to patients with intestinal insufficiency and prevent the need for parenteral nutrition. Overall, we hope that we can improve quality of life of patients that suffer from fecal fluid, electrolytes and macro- and micronutrient losses due to either intestinal mucosal disease or short bowel syndrome.

The AGEM international student fellowship 2023 (€500/month)

Anna Elizabeth Spiering

Sex differences in atherosclerosis

Atherosclerosis is the main cause of cardiovascular disease. Despite the well-recognized sexual dimorphism in clinical features of atherosclerosis, the underlying molecular mechanisms are unclear. Transcriptomic studies suggest that sex differences in the atherosclerotic plaque particularly locate to smooth muscle cells and endothelial cells. Furthermore, sex differences may be mediated by sex hormones as well as sex chromosomes. During my internship at UCLA, I crossed the Four Core Genotype mouse model into a high-cholesterol mouse model. The Four Core Genotype is a unique mouse model to tease apart the relative contributions of sex chromosomes and gonadal hormones to observed sex differences. The plaques from these mice will be subjected to single-cell RNA sequencing to shed more light onto the different components of sex in the plaque transcriptome.

Additionally, we knocked down X and Y chromosomal genes in cultured human smooth muscle and endothelial cells to test their role in various atherosclerosis-related assays. We found a causal relationship for X escape genes with in vitro smooth muscle cell calcification which may relate to observed clinical differences in plaque calcification. Results from this work will contribute to a better understanding of the mechanisms in sex differences in atherosclerosis, and eventually to a better treatment of atherosclerosis in both men and women.

Julia Menso

The Worldwide Standard in Mastery of Robotic Pancreatoduodenectomy – How to Get There

Robot-assisted pancreatoduodenectomy (RAPD) has developed rapidly over the past decades. RAPD aims to improve intra- and postoperative outcomes as compared to open and laparoscopic PD. In the Netherlands, the nationwide LAELAPS-3 training program was launched by the Dutch Pancreatic Cancer Group in all 8 high-volume centers with help of proctors originating from the University of Pittsburgh Medical, USA, resulting in RAPD implementation with currently 25% of all procedures being performed robotically. Despite similar techniques and well-defined outcomes, the incidence of postoperative morbidity and mortality following RAPD varies in centers worldwide. Hence, the Transatlantic Robot Pancreas Consortium was initiated to elucidate the etiology of observed international discrepancies in postoperative outcomes following RAPD for all indications, to subsequently improve international patient outcomes. The study includes three phases: 1) Retrospective data collection of RAPD outcomes and comparison of these rates between the participating centers, 2) Identification of differences in patient selection, perioperative care, intervention technique details, and complication registration, and 3) Assessment of the impact of the observed differences on complication rate and its feasibility and safety for implementation (evidence-based or with expert opinion/international consensus). This collaboration ultimately aims to establish an international consensus on the best practice of RAPD.

Lisa Zürcher

"Investigating the effect of diverse combinatory drugs in hepatocellular cancer derived organoids"

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. HCC is an aggressive cancer and often not diagnosed until an advanced stage. Treatment options are limited with only a few FDA-approved drugs available for advanced HCC on the market. Sorafenib, regorafenib and lenvatinib are multikinase inhibitors used for HCC treatment, but they exhibit a high non-response rate. The lack of effective therapies for HCC underscores the importance of suitable pre-clinical models for drug discovery and development. Traditional cell culture falls short in capturing the tumor biology accurately. The Heim group has established a method to create patient derived organoids out of HCC needle biopsies. These HCC patient derived organoids robustly retain the histological and genomic features of the originating tissue and thus can be adopted as in vitro surrogates of individual tumors representing the heterogeneous HCC patient population. Our main goal is to identify a novel drug combination with a broad effect in HCC, using our HCC patient derived organoids. We previously identified a set of FDA-approved drugs with anti-HCC activity in HCC organoids. These will be combined with standard-of-care treatments for HCC to uncover novel combinations with enhanced effects.

The aim of this study is to generate compelling preclinical evidence for a therapeutic strategy involving personalized drug combination therapy, serving as a proof-of-concept in patients with HCC.

Anna Ferrer

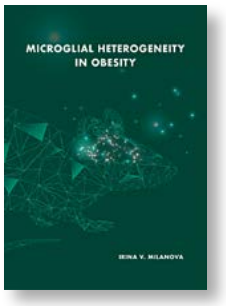
Exploring the interplay between lysosomal function and Senescence-Associated Beta-Galactosidase in omental and subcutaneous adipocytes

Cellular senescence is an irreversible block of cell cycle progression that can be triggered by an array of stressors such as oncogene activation, DNA damage or telomere shortening. Historically, senescence has been recognized as a beneficial and protective mechanism against tumorigenesis, or as a promoter of wound healing and tissue repair. However, recent studies have described a pathological role of senescence in adipocytes that can lead to metabolic dysfunction and adipose tissue inflammation. The hallmarks of senescent cells are often tissue and cell-type-specific, however, some changes exhibit consistent patterns across different cell types, such as increased lysosomal biogenesis and senescence-associated beta-galactosidase (SABG) activity. Lysosomes play a crucial role in cellular homeostasis through the autophagy-lysosomal pathway where macromolecules are degraded, cleared, or recycled within the cell. Preliminary findings in mature human adipocytes show increased lysosomal content in subcutaneous adipocytes compared to omental adipocytes, which is in line with that senescence has only been described in subcutaneous adipocytes.

This study will compare subcutaneous and omental adipocytes from the same patients to elucidate the differences in lysosomal attributes – content, biogenesis, maturation, and activity – and their relation to senescence. Senescence and lysosomal markers will be assessed using western blot, SABG-activity, and quantitative confocal microscopy. A better understanding of the crosstalk between lysosomes and senescence in obesity can lead to better predictors of obesity-associated metabolic comorbidities and the development of therapeutics to ameliorate the effects of senescence.

The AGEM contribution printing costs of theses 2023 (€250)

Irina Milanova



Date of defense: January 13th, 2023

Microglial heterogeneity in Obesity

The findings presented in this thesis provide evidence that microglia – the resident immune cells in the brain, have a heterogeneous nature in obesity regarding the time of day, brain region, sex and age. Moreover, we found that novel and optimized experimental approaches such as ultrasensitive proteomics and thermal proteome profiling allow us to gain a better understanding of these differences. These findings bring us closer to understanding the role microglia play during the progression of obesity.

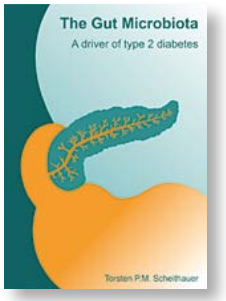
Tineke de Jong

Date of defense: March 17th, 2023

Premature aging of the stromal microenvironment in rheumatoid arthritis: Towards prevention of disease by targeting cellular aging

This thesis on rheumatoid arthritis (RA) describes the metabolic and aging phenotype of stromal cells from lymph nodes and synovium of RA patients and individuals at risk of developing disease. We showed that cellular aging and several metabolic alterations can already be detected before clinical onset of RA and might be responsible for the altered cellular behavior of these cells. Age-associated characteristics were partially restored by interventions targeting stromal cells and show potential for further exploration.

Torsten Scheithauer

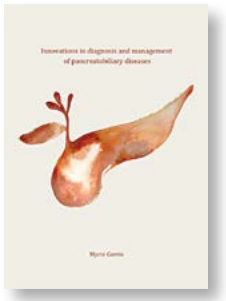


Date of defense: February 10th, 2023

The Gut Microbiota - a driver of type 2 diabetes

The studies described in this thesis investigated how changes in the gut microbiota relate to the development of type 2 diabetes. A western diet, which is usually rich in saturated fats, leads to changes in gut microbial composition. Altered intestinal microbial composition promotes obesity by increasing gut permeability, which in turn facilitates the translocation of bacterial components into blood circulation. Thereby, the gut microbiota can impact the function of several organs.

Myrthe Gorris

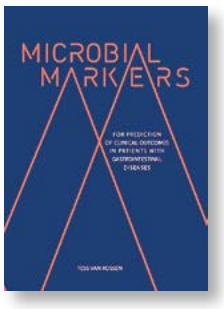


Date of defense: March 31st, 2023

Innovations in diagnosis and management of pancreatobiliary diseases

Pancreatobiliary diseases compromise a heterogeneous group of lesions, ranging from benign to malignant entities. The aim of this thesis was to improve diagnosis and management in these patients, with a specific focus on pancreatic cystic neoplasms. This thesis describes the results of an international study on spleen-preserving distal pancreatectomy in patients with intraductal papillary mucinous neoplasms and describes the results a randomized trial which investigated the sensitivity of brush cytology during endoscopic retrograde cholangiopancreatography.

Tessel van Rossen



Date of defense: April 6th, 2023

Microbial markers for prediction of clinical outcomes in patients with gastrointestinal disease

In this thesis I have investigated whether the intestinal microbiota composition can be used to predict clinical outcomes in patients with various gastro-intestinal diseases such as inflammatory bowel disease (Crohn's disease and ulcerative colitis), Clostridium difficile infection and esophageal cancer.

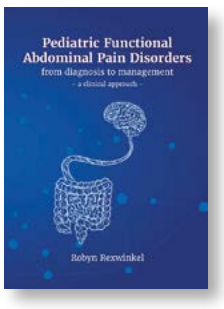
Ulrika Boulund

Date of defense: May 12th, 2023

Exploring high dimensional data in health and disease: from genome to microbiome

The molecular understanding of human health and disease has greatly improved with the advance of modern technologies for measuring the human genome, gene expression, metabolites, and microbiome. However, many relationships between the human organism, the microscopic organisms within us, and our lifestyle are still unknown. In this thesis we made use of large data from multiple populations to further our understanding of this complex interplay in health and disease

Robyn Rexwinkel

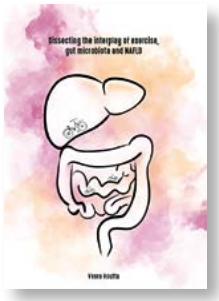


Date of defense: April 14th, 2023

Pediatric Functional Abdominal Pain Disorders: from diagnosis to management – a clinical approach

Functional abdominal pain is common in pediatrics and characterized by chronic abdominal pain (≥2 months) and alterations in stool pattern. It is associated with decreased quality of life and school attendance, but the pathophysiology is not completely understood and diagnosis is generally symptom-based. This thesis describes novel insights regarding diagnostic and management strategies, shared decision making and clinical outcome measures for research, with the aim to enhance patient care, improve quality of care, and allow better evidence-based decision making.

Veera Houtta

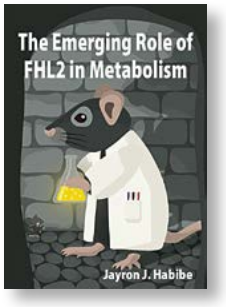


Date of defense: June 9th, 2023

Dissecting the interplay of exercise, gut microbiota and NAFLD

The cornerstone treatment for NAFLD is lifestyle management but the evidence on the effect of exercise on advanced stages is not fully elucidated. In addition, it is not known how gut microbiota is related to NAFLD and exercise. Therefore, this thesis investigated the effect of exercise on NAFLD and whether the effect if mediated by gut microbiota and metabolites. The work warrants longer, and larger exercise interventions to validate the present guidelines for exercise management.

Jayron Habibe

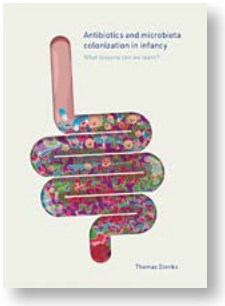


Date of defense: June 14th, 2023

The emerging role of FHL2 in metabolism

This thesis focuses on understanding the role of the protein FHL2 in metabolic diseases like Type 2 diabetes and obesity. FHL2 is made up of LIM domains, and it interacts with proteins in our body, influencing processes like tumour development and bone development.
The author investigated FHL2's involvement in glucose regulation, obesity, genetic variations, and its impact on blood vessel function, and presented their findings in this thesis

Thomas Dierikx



Date of defense: June 23rd, 2023

Antibiotics and microbiota colonization in infancy: What lessons can we learn?

In the thesis titled "Antibiotics and microbiota colonization in infancy: What lessons can we learn?" the effect of antibiotic use during childbirth on the microbiome of the child is described. Blood tests are also being investigated to reduce antibiotic use in newborn babies. In addition, the protective role of probiotics during antibiotic use is being investigated.

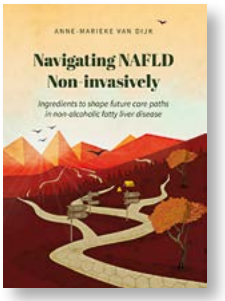
Charlotte Verburgt

Date of defense: June 16th, 2023

Unravelling the microbiome in paediatric Crohn's disease: A journey towards personalised therapy

Crohn's Disease is a chronic inflammatory disease that affects children in crucial developmental stages of their life. Understanding disease mechanisms is therefore vital in search for effective treatments in order to achieve optimal disease control. With this thesis, we aimed to unravel the role of the microbiome in Paediatric Crohn's Disease (CD). By studying the microbiome including its changes induced by treatment, we developed a predictive model for risk-assessment of relapse in the first year after diagnosis. In a clinical study, we then applied this model to provide the first steps towards personalised treatment in paediatric CD

Anne-Marieke van Dijk



Date of defense: June 30th, 2023

Navigating NAFLD Non-invasively: Ingredients to shape future care paths in non-alcoholic fatty liver disease

The prevalence of non-alcoholic fatty liver disease (NAFLD) is increasing worldwide, including the advanced stages: NAFLD fibrosis, cirrhosis and hepatocellular carcinoma. This thesis outlines the wide range of liver test candidates to diagnose and stage NAFLD non-invasively. This broad spectrum of non-invasive liver tests may perform varyingly in a diverse population. Therefore, it is key to select the optimal test for any particular patient. This selection process should be implemented in NAFLD care paths.

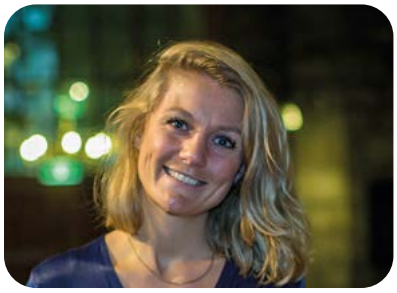
Robin Erken

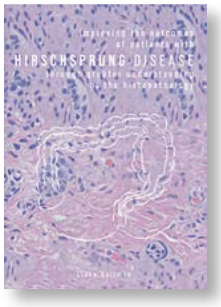
Date of defense: June 30th, 2023

Towards a functional cure for chronic hepatitis B

This thesis focuses on several aspects that contribute to the development of a functional cure in patients with chronic hepatitis B (CHB). This includes an analysis of the immunological response of patients to an acute infection. Second, we evaluated new markers for CHB and mapped to which extend integration of the virus into the human genome differs between patients. Finally, we describe the effect of different treatments against CHB on safety and efficacy.

Lieke Beltman



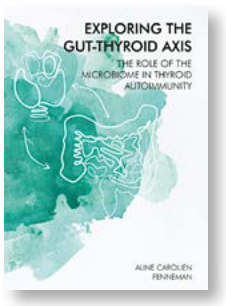


Date of defense: September 29th, 2023

Improving the outcomes of patients with Hirschsprung Disease through greater understanding of the histopathology

This thesis contains eight chapters related to children born with Hirschsprung's disease where the histopathology and clinical implications are discussed in depth. Conclusions from the thesis are: before surgery, children with a completely diseased colon are more likely to develop complications and we recommend that they be operated on as soon as possible, flushing the colon after surgery can suffer life-threatening complications therefore we recommend a temporary tube over the attachment.

Aline Fenneman



Date of defense: September 15th, 2023

Exploring the Gut-Thyroid Axis: The Role of the Microbiome in Thyroid Autoimmunity

The research in this thesis was aimed to shed new light on the bidirectional relationship between the gut and the thyroid gland and its clinical consequences in autoimmune thyroid diseases. It comprises a comprehensive review of the current literature, an epidemiological study, a randomized clinical trial, and basic research. Together, these studies can be seen as the beginning of an ongoing exploration of the emerging field of gut microbiota research in relation to thyroid health.

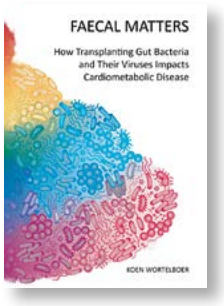
Adriaan Volkers

Date of defense: October 19th, 2023

Alternatives in the management of inflammatory bowel disease

In this thesis, we focus on optimizing inflammatory bowel disease (IBD) management through alternative monitoring and treatment methods. It also examines the implications of SARS-CoV-2 for patients with immune-mediated inflammatory diseases, including IBD. The research includes studies on pan-enteric capsule endoscopy for Crohn's disease, fecal biomarkers for pediatric CD, point-of-care testing devices, and a successful mercaptopurine treatment trial. Additionally, it explores transitioning from intravenous to subcutaneous vedolizumab injections and the impact of immunosuppressive agents on SARS-CoV-2 immunity in IMID patients.

Koen Wortelboer

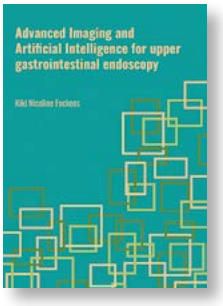


Date of defense: November 2nd, 2023

Faecal matters: how transplanting gut bacteria and their viruses impacts cardiometabolic disease

This thesis explores the potential of the gut microbiota in cardiometabolic diseases, a growing global health concern. Faecal microbiota transplantation is increasingly used as experimental treatment with mixed results. Although recruitment of eligible stool donors is challenging, this intervention provides an opportunity to study the gut microbiota's interaction with its human host, and has led to the discovery of new beneficial microbes. Furthermore, bacteriophages can shape bacterial communities and their contribution to disease warrants further investigation.

Kiki Fockens

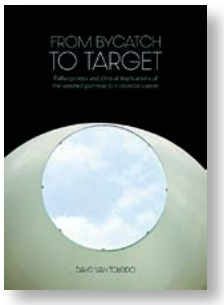


Date of defense: November 8th, 2023

Advanced Imaging and Artificial Intelligence for upper gastrointestinal endoscopy

This thesis describes the improvement of the visualization and detection of early neoplasia in the upper gastrointestinal tract using endoscopy. Advanced imaging techniques improve the visualization of neoplasia in both the esophagus and the stomach. Furthermore, the use of artificial intelligence can assist the endoscopist to detect neoplasia in a Barrett's esophagus at an early stage. A computer-aided detection (CADe) system appears to outperform general endoscopists in the detection of early Barrett's

David van Toledo

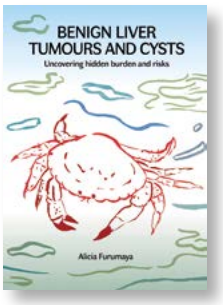


Date of defense: November 3rd, 2023

From bycatch to target: pathogenesis and clinical implications of the serrated pathway to colorectal cancer

Prevention of colorectal cancer (CRC) could be established by detecting and removing its precursors: colonic polyps. Besides adenomas, up to 30% of all CRCs arise via the serrated pathway. Since two decades, serrated polyps are no longer considered as innocent bycatch of colonoscopy, but evidence showed that these are potentially malignant polyps that should be removed. Our understanding of serrated polyps is overdue. In this thesis, we aimed to expand our understanding of the pathogenesis and clinical implications of the serrated pathway.

Alicia Furumaya



Date of defense: November 10th, 2023

Benign liver tumours and cysts: Uncovering hidden burden and risks

This thesis focuses on benign liver tumours and cysts (BLTC), such as hepatocellular adenoma, focal nodular hyperplasia, liver hemangiomas, and simple liver cysts. The goal was to better understand the symptoms experienced by patients and the risks associated with BLTC. A set of patient-reported outcome measures (PROMs) was developed and will be used in a prospective study. Next-generation sequencing was found to have additional value in detecting high-risk mutations in hepatocellular adenoma.

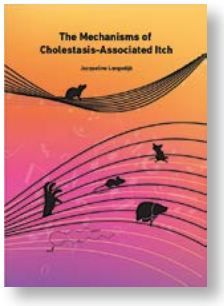
Tessel Boertien

Date of defense: November 13th, 2023

Novel diagnostic and therapeutic options in pituitary adenoma – an enlightening approach

This thesis addresses several clinical questions regarding pituitary tumours. The first chapters describe observational studies in patients with various sellar masses requiring surgical resection. These studies focus on complaints of headache and tinnitus, and on consequences of optic nerve compression on the pupillary light response, the biological clock, and retinal thickness. The final chapters are centred around the GALANT trial: an intervention trial on the effect of lanreotide in patients with a non-functioning pituitary macroadenoma.

Jacqueline Langedijk

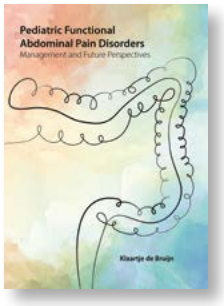


Date of defense: November 29th, 2023

The Mechanisms of Cholestasis-Associated Itch

Itch is one of the most frequent symptoms in patients with chronic cholestatic disorders. During cholestasis (diminished or impaired bile flow), serum levels of the enzyme autotaxin (ATX), but also serum levels of bile salt-like compounds are increased. We measured ATX activity and expression under the influence of those compounds. Additionally, we measured scratch activity in different cholestatic mouse models and we screened the bile from patients for itch-inducing compounds.

Klaartje de Bruijn

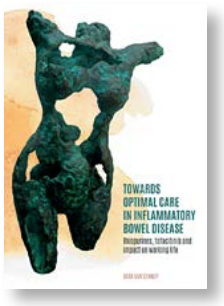


Date of defense: November 23rd, 2023

Pediatric Functional Abdominal Pain Disorders - Management and Future Perspectives

Functional abdominal pain disorders (FAPDs) are common chronic conditions among children and adolescents. FAPDs are characterized by long lasting abdominal pain, where the gastrointestinal symptoms cannot be fully explained by another medical condition after appropriate clinical evaluation. In this thesis, we focused on the clinical evaluation of patients in order to customize FAPDs management. Moreover, we described the different management strategies of FAPDs, including dietary interventions, non-pharmacological (psychosocial) and pharmacological treatment regimens

Sara van Gennep



Date of defense: December 7th, 2023

Towards optimal care in inflammatory bowel disease: Thiopurines, tofacitinib and impact on working life

The care for inflammatory bowel disease (IBD) patients is challenging. Although already great progress has been made in the field of IBD care, the rapid development of new drugs and shifting treatment targets also leads to new challenges to overcome. In this thesis, we aimed for further optimization of IBD care by evaluating efficacy and safety of 'old' and 'new' oral immunomodulators (thiopurines and tofacitinib) and by focusing on the disease impact on working life.

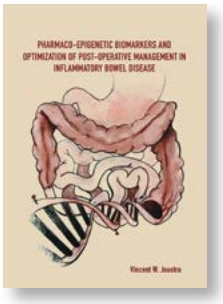
Nadine van Huijgevoort

Date of defense: December 15th, 2023

Pancreatobiliary diseases – improving diagnosis and outcomes

In the last decades, knowledge on pancreatic diseases has rapidly evolved. The founding of both the Dutch Pancreatitis Study Group and the Dutch Pancreatic Cancer Group (DPCG) have contributed significantly to improve diagnosis and treatment in pancreatic diseases. However, much still remains to be investigated, especially in patients with (pre) malignant pancreatic lesions. The general aim of this thesis is to further improve the understanding of (pre) malignant pancreatobiliary diseases as well as to further improve clinical outcome of patients suffering from these diseases.

Vincent Joustra

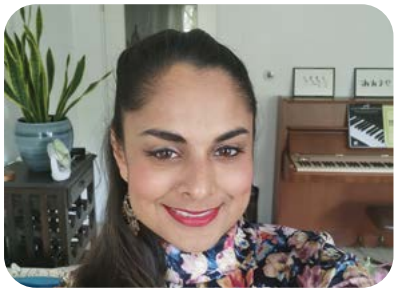


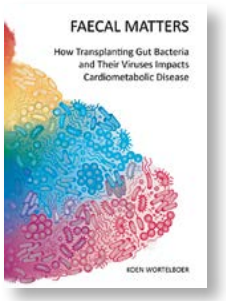
Date of defense: December 20th, 2023

Pharmaco-epigenetic biomarkers and optimization of post-operative management in inflammatory bowel disease

This thesis explores personalized therapy selection and postoperative treatment in inflammatory bowel disease (IBD). Part I identifies pharmaco-epigenetic biomarkers in peripheral blood of IBD patients, predicting endoscopic and clinical response to vedolizumab, ustekinumab, and tofacitinib using epigenetic models. Part II evaluates postoperative treatment in Crohn's disease, showing a cumulative effect of risk for early endoscopic recurrence, suggesting prophylactic medication for a small subset. Additionally, we show that epigenome-wide methylation analysis does not yield a definitive signal for personalized postoperative management.

Ishtu Hageman





Date of defense: December 20th, 2023

Novel biomarkers to guide therapy in chronic inflammatory diseases

In this thesis, we focused on the role of the epigenetic modifications in Inflammatory Bowel Disease (IBD) and other immune mediated diseases such as rheumatoid arthritis. In particular, we elaborated on aberrant DNA methylation and investigated its potential to predict therapy response to biological treatment. Furthermore, we explored other novel biomarkers to biological response with microbial signatures and single cell transcriptomics in IBD.

Anne Linde Mak

Date of defense: December 22nd, 2023

Metabolic dysfunction-associated steatotic liver disease: A wide-angled perspective on a multifaceted problem

In this thesis, several components relevant to metabolic dysfunction-associated steatotic liver disease (MASLD) are investigated. We identified new genetic alterations in individuals with MASLD, developed a novel biomarker panel to predict hepatic fibrosis in MASLD, and investigated the influence of the gut microbiome on MASLD through fecal microbiome transplantation (FMT) and murine studies. Together, this thesis provides new insights into the complexity of MASLD and offers potential routes to improve care for patients with MASLD.

Events 2023

AGEM seminar series 2023

AGEM Tager Lectures

The AGEM research institute has a seminar series in the Amsterdam UMC, location AMC, focused on metabolism and endocrinology; the Tager Lecture, called after Professor Joseph Tager. Joseph Tager made important contributions to Fabry, Pompe and Gaucher disease and had a major impact on our understanding of peroxisomal diseases. He was chairman of the Biochemistry Department at the University of Amsterdam (1980-1991).
The Tager Lecture series is organized by AGEM PI's Riekelt Houtkooper, Susanne La Fleur, Noam Zelcer and Eveline Bruinstroop. Suggestions for future speakers for the Tager lecture are always welcome.

Thursday February 2nd, 2023 **Amsterdam UMC, location AMC**
Dr. Lena Parnas
Max Planck Institute for Biology of Ageing

"Organelle and metabolic dynamics of infection"

Thursday April 6th, 2023

Amsterdam UMC, location AMC

Prof. dr. Duncan Basset

Molecular Endocrinology Laboratory, Department of Metabolism, Digestion and Reproduction, Imperial College London

"Advances in understanding the skeletal consequences of thyroid disease"

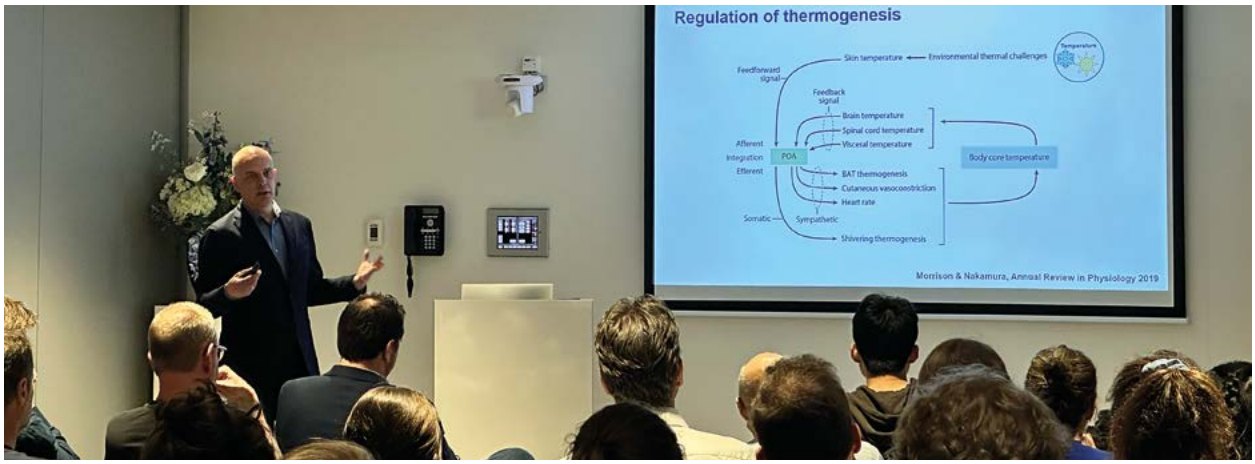
Thursday June 8th, 2023

Amsterdam UMC, location AMC

Prof. dr. Joerg Heeren

University Medical Center Hamburg-Eppendorf, Department for Biochemistry and Molecular Cell Biology

"Brown adipose tissue and lipid metabolism"



Thursday July 20th, 2023

Amsterdam UMC, location AMC

Prof. dr. Ron Heeren

The Maastricht MultiModal Molecular Imaging institute, Maastricht University

"Seeing is believing: visualizing cellular metabolism with imaging mass spectrometry"

Thursday September 7th, 2023

Amsterdam UMC, location AMC

Prof. dr. Jaap Keijer

Human and Animal Physiology, Wageningen University

"Functional and pathway changes in the human aging muscle"

Thursday November 9th, 2023 **Amsterdam UMC, location AMC**

Dr. Felix Hartmann

German Cancer Research Center (DKFZ), Heidelberg

"Quantifying metabolic regulation in tissue microenvironments via multiplexed imaging"

ImmunoMetNet Amsterdam UMC meetings 2023

Tuesday February 28th **Amsterdam UMC, location AMC, Vrijzaal**

After the first successful year of ImmunoMetNet Amsterdam UMC series on 2022, a new series got kicked off in February 2023 at the AMC side for the first time. With an attendance of more than 25 people, many of them new faces joining the network for the first time, the afternoon was filled with very good scientific discussions around the 4 topics presented. Once again, the stage was reserved for young researchers, in this case:

- Nienke Goedhart (CCA/AII), PhD candidate in the lab of Eric Eldering & Arnon Kater shared her work on decreased mitochondrial metabolism as the driver of T-cell dysfunction in chronic lymphocytic leukemia.
- Iosifina Foskolou (AII/Sanquin), recently incorporated as PI in Sanquin, presented her project about the two enantiomers of 2-hydroxyglutarate and how they differentially regulate cytotoxic T cell function.
- Frouwkje Politiek (AGEM/AII), PhD candidate in Hans Waterham lab presented her work on the mechanisms underlying inflammation in mevalonate kinase deficiency.
- Chiara Montironi (CCA/AII), PhD candidate also in the lab of Eric Eldering and Arnon Kater showed her work on how leukemic cells suppress T cell function by inducing pseudohypoxia and autocrine purinergic signaling.

The afternoon closed with a wonderful borrel provided by AGEM, which is always a great opportunity to continue the discussions in a low-key format, one of the goals of these meetings. Besides, by organizing this event at location AMC this time, the aim of making the ImmunoMetNet network wider between both locations was further accomplished.

Wednesday November 8th **Amsterdam UMC, location VUmc, O|2 building**

The last ImmunoMetNet AUMC meeting of the year took place at the VUmc side where it could be observed that this community is getting consolidated and grows. We counted with the presentations by four new young speakers:

- Chun-Xia Yi (AGEM/AII) presented the work of her PhD candidate, Han Jiao, who was scheduled but couldn´t make it to the meeting, about the role of microglia in time restricted feeding.
- Jasper Sanders (CCA), PhD candidate in the group of Sarah Derks shared his work using spatial transcriptomics to identify metabolic dysregulation as one of the main drivers of immune suppression in esophageal adenocarcinoma.
- Signe Mosegaard (ACS/AGEM), postdoc in the group of Riekelt Houtkooper, shared her research about human inborn errors of long-chain fatty acid oxidation and their relation to impaired inflammatory responses to TLR4-ligand LPS.
- Alexandros Nianias (CCA), PhD candidate at the lab of Maria Themeli, shared their model of iPSC-derived T cells and explained how reprogramming the metabolic state of this cells can be used to generate better off-the-shelf CAR-T cells.

Keep an eye on www.immunometnet.com and the @immunometnet Twitter profile or reach out to immunometnet@amsterdamumc.nl for more information on future ImmunoMetNet seminar series!

Grand Rounds in Digestive Diseases 2023

From the origins of colorectal cancer, to duodenal resurfacing for the treatment of diabetes or spatial omics to decipher the role of macrophages in liver disease. These are just a few examples of the series of lectures organized by the Department of Gastroenterology & Hepatology, entitled 'Grand Rounds in Digestive Diseases'.

In bi-monthly Thursday morning sessions, top-level scientists from the Amsterdam UMC and beyond provide a broad audience with an overview of the recent scientific advances in their research field. In addition to purely scientific Gastroenterology & Hepatology-related presentations, four times a year more general topics are covered.

These series of lectures have been initiated by Prof. Geert D'Haens and Dr. Joep Grootjans from the department of Gastroenterology & Hepatology, together with the research institute AGEM (Amsterdam Gastroenterology Endocrinology Metabolism). Topics are selected by a steering committee which includes clinical and basic scientists from the departments of Surgery, Paediatrics, Radiology, Pathology and the Tytgat Institute. The Grand Rounds are hosted both on-site at the location AMC (bi-monthly, Thursday morning from 8.00AM to 8.45AM) and online via zoom.

January 12th, 2023	Joep Bartelsman ***Four decades of gastrointestinal endoscopy in Amsterdam" Memorial Lecture for Prof Kees Huibregtse***
January 26th, 2023	Max Nieuwdorp ***The impact of microbiome and microbiome modulation on systemic diseases***
February 9th, 2023	Regina Beets-Tan ***Modern imaging of Colorectal cancer***
February 23rd, 2023	Marca Wauben ***The unknown messengers of the body: extracellular vesicles***
March 9th, 2023	Saskia Peerdeman ***Data-driven and digital learning, future perspectives***
April 6th, 2023	Bas Oldenburg ***Colitis-associated neoplasia***

April 20th, 2023	Sven Francque ***Vascular alterations in NASH pathophysiology***
June 1st, 2023	Cyriel Ponsioen ***PSC, an orphan groing up***
June 15th, 2023	Joep Derickx ***Intestinal anastomotic healing and leakage***
June 29th, 2023	James Kinross ***iEndoscope – towards real time precision metabolic phenotyping in the operating room***
September 9th, 2023	Robert Porte ***Why bile ducts continue to be the Achilles' heel of liver transplantation and what we can do about it***
September 21st, 2023	Johan van Limbergen ***Optimizing nutritional therapy of IBD***
October 5th, 2023	Joost Drenth ***Angiodysplasieën, from start to finish***
October 19th, 2023	Roos Pouw ***Unethical or unprecedented: novel management strategies for high-risk esophageal adenocarcinoma***
November 2nd, 2023	Geert Kazemier ***Gastrointestinal Cancer Care: Connecting the Dots***
November 16th, 2023	Anne Griffiths ***Revisiting treatment algorithms in paediatric Crohn's disease***
November 30th, 2023	Gerd Bouma ***Celiac disease***
December 14th, 2023	Jan Paul Medema ***A view to a kill; the balance between life and death in the intestine***

Site visit external committee for AGEM's institutional evaluation

Site visit

November 29th & 30th, 2023 **Amsterdam UMC**

November 29 and 30, 2023, an external committee came to the Amsterdam UMC for a site visit, to complete the institutional evaluation of Amsterdam Gastroenterology Endocrinology Metabolism (AGEM) over the period 2017-2022 according to the Strategy Evaluation Protocol (SEP) 2021-2027.

The committee consisted of Prof. dr. Daisy Jonkers, Scientific Director of the NUTRIM research institute and Professor of Intestinal Health, Maastricht University; Melanie Modder MSc, PhD candidate, Leiden UMC; Prof. dr. Jörg Heeren, Department of Biochemistry and Molecular Cell Biology, UKE Hamburg; Jeroen van Kempen, chair of European Galactosaemia Society (EGS) and former chair of Galactosemie Vereniging Nederland (GVN); Prof. dr. Verena Keitel, Head of Dept. of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke-Universität, Magdeburg; Prof. dr. Jens Mittag, Professor in Molecular Endocrinology at the Center of Brain, Behavior and Metabolism, University of Lübeck and Prof. dr. Chris Probert, Professor of Gastroenterology, University of Liverpool. Dr. Fiona Schouten was independent project manager and secretary to the committee.

The site visit days were filled with relatively formal interview sessions on the following topics: AGEM general, talent development, PhD policy and training, societal relevance, gastroenterology, endocrinology, and metabolism. Based on these interviews and AGEMs self-evaluation report, the committee wrote an assessment report, including reviews of the mentioned topics and several recommendations for the future.

AGEM annual retreat

March 30th & 31st 2023

AGEM retreat 2023

Bilderberg Hotel 't Speulderbos, Garderen

The goal of the AGEM retreat is to discuss, share and learn from each other's research. Mixing AGEM retreat customs with new ideas, definitely resulted in successfully obtaining this AGEM vision. It was absolutely fantastic to see all the PhD candidates, postdocs and PIs together and enjoying this event!

For a lot of PhD candidates this was their first conference, which again resulted in a large number of participants. It was wonderful to be able to have this meeting together and network with and learn from each other.

We had a full and diverse program. Due to the large number of participants, who we all wanted to give the opportunity to present their work, we had three plenary sessions as well as two parallel sessions (consisting of four sessions each). New this year was the poster session organized on Thursday, to give participants the opportunity to give a pitch and have a lively discussion with attendees. Many interesting classical presentations, elevator pitches and poster presentations within the fields of gastroenterology, endocrinology & metabolism were given by our colleagues. New this year was the best publication battle. Charlotte van Veldhuisen won a cheque of €250.

Next to these lectures, the attendees could choose a workshop to attend from an array of relevant topics. The options offered this year were: "PopArt painting", "Speed Reading", "Eat your bugs" and "How to foster research integrity?".

To get to know each other better, we organized a fun and interactive evening program. After dinner, Dr. Garmt Dijksterhuis, specialized in psychological and perception research, gave an interactive lecture on how we experience and perceive food. The first day ended with a good party themed 'Under Water'. Everybody excelled in their outfits and dance moves; it was incredible to see the great effort participants had made to match their outfits to the retreat's theme.

Friday morning started with the opportunity to go for a swim at the hotel's (indoor) swimming pool and start the second day of the retreat refreshed and energized.

This year's out of the box speaker was Else de Ridder, who gave a very inspiring lecture on how to reduce, reuse and recycle products at your own workplace. The keynote speaker on Friday, Prof. Dr. Renger Witkamp gave us insights on nutrition and pharmacology. By using a restaurant menu, he gave us information on nutritional assessment strategies and examples of nutritional interventions.

Last but not least we would like to congratulate those who won an award: Heleen Jansen for best presentation, Lisanne Pattynama for best poster presentation, Naomi Waieser for most contributing participant and Khya Snelder for best party outfit.

Thank you all for making this a great AGEM retreat in 2023. We look forward to see you again, and to welcome new participants in 2024!

On behalf of the Organizing Committee,
Soumia Majait & Anouk Olthof


Purpose
Addressing and embedding sustainability in Amsterdam UMC
• Bottom-up: enthuse employees and encourage and support them to start initiatives
• Top down: discussing with management on how to integrate sustainability in the organization
Amsterdam Gastroenterology Endocrinology Metabolism


Charlotte Teunis
Klevis Ndoj

AGEM meetings 2023

Thursday June 15th, 2023 Symposium: "ImmunoMetNet" supported by AGEM

Amsterdam UMC, location VUmc, O|2 building

The new edition of the Annual ImmunoMetNet was held this year at the auditorium of the O2 building. More than 100 researchers from different institutes all across the country joined for what is officially consolidated as the national reunion of groups working on immunometabolism.

The day was kicked off with the session dedicated to metabolic control of the immune system by the keynote speaker Rajkumar Savai (Max Planck Institute for Heart and Lung Research, Germany) and his talk about how IRG1/ itaconate axis regulates lung tumorigenesis via pentose phosphate pathway. Next was the short presentation by the young researcher Eline Brombacher, PhD student in Bart Everts lab (LUMC), about AMPK control of DC tolerogenicity through rewiring of lipid metabolism. Closing the first session, Leila Akkari (NKI) presented the work of her group on metabolic rewiring in the brain tumor microenvironment, with a focus on macrophages.

After a nice coffee break, Anna Schurich (King's College London, UK) opened the second morning session, which was dedicated to molecular immunometabolism. She shared their last data on co-stimulatory domains as drivers of metabolic regulation of CAR T cell function. After that, Henk Schipper (UMC Utrecht) presented a project where they study lipoproteins as vesicles for lipid antigen delivery and activation of invariant Natural Killer T cells. The third presentation was by Sander van Kasteren (Leiden University) about click chemistry-based methods to add a nutrient dimension to complex flow cytometry.

An excellent lunch provided by AGEM secured, once again, the fuel to very nice interactions between the speakers of the two sessions in the morning and the other attendants, giving place already to new collaborations! It was also a good moment for students from different labs to interact with each other and exchange thoughts and opinions not only about the talks but also about future career development.

In the afternoon, the third session about Immunometabolism in health and disease was kicked off by Niels Eijkelkamp (UMC Utrecht) with a talk about positive energy and how the immune system resolves inflammatory pain. It was followed by a short talk by Chiara Geyer, postdoc in Jeroen den Dunnen's lab (Amsterdam UMC), on the identification of the metabolic pathways that underlie hyper-inflammation by human alveolar macrophages in severe COVID-19. The third and last speaker of the session was Bruno Guigas (LUMC) who shared the work of his group on the role of glycans and lectins in the crosstalk between metabolic and immune cells.

After a coffee break, the last session of the day brough the topic of immunometabolites into the stage with first a presentation by Enric Mocholi-Gimeno, postdoc in Paul Coffer's lab (UMC Utrecht) regarding fueling T cell activation and the essential role of pyruvate dehydrogenase in acetyl-CoA production. Next, Anaisa Valido Ferreira, postdoc in the lab of Mihai Netea (Radboud UMC) presented her work on dimethyl itaconate and how it induces long-term innate immune responses. To close the meeting, we had the pleasure of having Randall S Johnson (University of Cambridge, UK) as keynote speaker. He provided an overview on the role of oxygen and immunometabolites in shaping immune function.

Jan van den Bossche, first organizer of ImmunoMetNet in 2019, closed the meeting by announcing the consolidation of the European ImmunoMetabolism Network with a meeting next year in Copenhagen from 26 to 28th June, which was received with high enthusiasm by all participants! Keep an eye on the Twitter profile @immunometeurope for more info.

Thursday October 5th, 2023 AGEM PI event "Food for Life"

Volkshotel in Amsterdam

On Thursday October 5th, 2023, twenty AGEM researchers came together to discuss their research related to "Food for Life". The Amsterdam UMC Food for Life initiative aims to create a cross-cutting research line around food that unites all eight Amsterdam UMC research institutes, and covers food as medicine, food as part of care, food for prevention and food for planetary health

The aim of the evening was to find thematic connection and synergies specifically within AGEM. Firstly, Ric van Tol, AGEM's dedicated business developer, introduced the Amsterdam UMC Food for Life initiative to the attendees. Thereafter, researchers that were invited to present, informed the others on the existing research through various pitches that could be loosely grouped into three themes: Food for Adults, Food for Children and Food in Hospitals.

This resulted in talks about perioperative and time-restricted feeding, and the effect of nutrients on children and adults with MASLD, chronic bowel inflammation, chronic intestinal failure, inborn errors of metabolism and other metabolic diseases. It was inspiring to see that many researchers were already collaborating on their research, crossing departmental boundaries. After these presentations, more in depth discussions and networking were facilitated during a walking dinner with delicious bites that paired perfectly with the theme of the evening. Based on the enthusiastic feedback from the participants afterwards, the event was a success and hopefully a starting point for further collaborations.

December 8th, 2023 AGEM – CCA symposium: "HPBetter Symposium 2023 / Together we can make HPB treatments better"

O|2 building, Amsterdam UMC and online

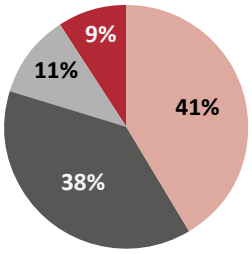
Numbers and Facts 2023

AGEM finances 2023

For 2023, the AGEM research institute was provided with €559.253 (€253.838 from VUmc and €305.415 from AMC). In the table below is shown how this money spend. Most of the 2023 budget was used for the AGEM grants.

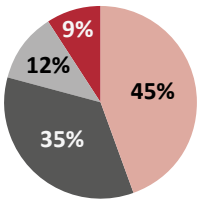
Income 2023	
AMC	€ 305.415,00
Vumc	€ 253.838,00
Total	**€ 559.253,00**

Expenditure 2023



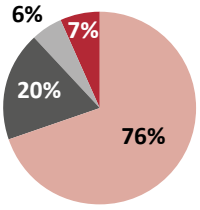
Income 2022	
AMC	€ 305.415,00
Vumc	€ 251.251,00
Total	**€ 556.666,00**

Expenditure 2022



Income 2021	
AMC	€ 308.500,00
Vumc	€ 235,789,00
Total	**€ 562.289,00**

Expenditure 2021



AGEM grants *Personnel* *Meetings* *Miscellaneous*

AGEM numbers 2023

AGEM researchers

Information about the number of researchers affiliated with AGEM was collected using the Research Information Systems Pure VUmc and Pure AMC in April, 2024, the AGEM administration and Hora Finita for VUmc PhD candidates. Registration of research institute affiliation was done by the researchers themselves, by representatives of the department of the researcher, by personnel from the Medical Library AMC or by the policy officer of the AGEM research institute. Researchers affiliated with AGEM registered in the VUmc and AMC Pure instances have been combined and deduplicated.

	2021	2022	2023
Principal Investigators	99	101	87
PhD candidates	432	415	484
Other researchers	221	214	215
Total AGEM researchers	**752**	**730**	**786**

AGEM publications

The reported data include all published research output as registered in the Research Information Systems Pure VUmc and Pure AMC in April, 2024. Research output of all researchers affiliated with AGEM are included. Publications are ascribed to AGEM based on the affiliations of the authors. A publication can be ascribed to one or more research institutes depending on the affiliations of the authors. Publications registered in the VUmc and AMC Pure instances have been combined and deduplicated. PhD-theses are ascribed to AGEM based on the affiliations of the (co-)supervisors. A thesis can be ascribed to one or more research institutes depending on the affiliations of the (co-)supervisors.

	2021	2022	2023
Refereed articles	1532	1429	1301
PhD theses	77	90	120
Other publications	178	88	101
Total AGEM publications	**1787**	**1607**	**1522**

Appointed professors 2023

Prof. dr. Elena Levtchenko
Translational Nephrology

On May 30th, 2023, Elena Levtchenko was appointed professor of Translational Nephrology at the University of Amsterdam. She works as a head of Pediatric Nephrology in Emma Children's Hospital and is a PI in the laboratory of Pediatric Nephrology, Amsterdam UMC.

Her research focuses on unraveling disease mechanisms and finding curative therapies for children with congenital nephropathies, using drug retargeting, gene and cell therapy. Being part of Emma Centre of Personalized Medicine, together with UD Fanny Arcolino, Levchenko aims to find cure for the metabolic disease cystinosis. She is a Medical Advisor for the Dutch and Flemish Cystinosis Patients Group and of the Cystinosis Network Europe.

By bridging the gap between fundamental science and clinical needs of the patients, Levtchenko's lab discovered a new type of kidney stem cells in urine of preterm neonates. These cells can be isolated non-invasively and represent a unique tool for kidney-targeted cell therapy and personalized medicine.

Levtchenko has an extensive international network; she leads a Working group on Metabolic and Stone-forming disorders of the European Reference Kidney Network and is a chair of the Educational Committee of the European Society for Pediatric Nephrology (ESPN). She is a council member of the International Pediatric Nephrology Association (IPNA) and is an Associate Editor of Pediatric Nephrology Journal. She is a holder of the European Research Council (ERC) Consolidator Grant.

Prof. dr. Joost Drenth
Hepatology

On May 30th, 2023, Joost Drenth was appointed professor of Hepatology. As of September 1st 2023, Joost is a hepatologist with the Department of Gastroenterology & Hepatology at Amsterdam UMC. He is the former chair of the Department of Gastroenterology & Hepatology at the Radboudumc.

Prof. Drenth has a long term research interest in rare (liver) disorders with a clear focus to improve quality of life of these patients. He has an interest polycystic liver disease and developed tools and management options to better manage the disease such as novel treatment paradigms, development of a validated questionnaire and tools such as automated liver volumetry to evaluate the efficacy of treatment strategies. He initiated >50 rigorous clinical trials in many rare diseases such as hereditary angiodysplasias, autoimmune disorders, polycystic liver disease, and polycystic kidney disease amongst others. This opened up the road for novel treatment options for patients living with a rare disease.

He has been at the root of the European Rare diseases Network (ERN) Rare Liver consortium where Amsterdam UMC acts as a collaborative partner. He is the current Editor-in-Chief of the United European Gastroenterology (UEG) Journal and was elected to become UEG's Vice President (2024).

Prof. dr. Joep Derikx

Pediatric surgery; compromised gut in neonates and children

On October 17th, 2023, Joep Derikx was appointed professor of pediatric surgery; compromised gut in neonates and children. Joep Derikx is a pediatric surgeon and Amsterdam UMC Principal Investigator with a special interest in translational research that is in line with his clinical expertise. This comprises the care for neonates and children with a complex intestinal disease including necrotizing enterocolitis and Hirschsprung disease. The focus of his research is understanding the pathophysiology and early detection of aforementioned diseases. Furthermore he studies how intestinal anastomoses heal and why leakage occurs. Joep participates in several national and European consortia for patient care, research and development of guidelines. He generated a program for one-stop-shop pediatric inguinal hernia surgery in Amsterdam UMC and created a website for children and parents/caretakers on this topic (www.kinderliesbreuk.nl). Joep is very honored with his appointment as professor 'Compromised gut in neonates and children'.

Prof. dr. Jeroen Hermanides

Anesthesiology; perioperative metabolism

On October 17th, 2023, Jeroen Hermanides was appointed professor of anesthesiology, in specific perioperative metabolism, at the University of Amsterdam. Het delivered his inaugural lecture "Vooruitgang voor pessimisten" on April 12th 2024.

Jeroen Hermanides is an anesthesiologist with a PhD in clinical diabetology and also trained in neurometabolism during a Marie-Curie fellowship at the University of Cambridge, UK. He is part of the scientific committee of the Dutch Society for Anesthesiologists and coordinator in the bachelor curriculum at the faculty of medicine.

Jeroen's chair focusses on the metabolic changes during and after surgery and the treatment of diabetes mellitus in the perioperative period. Furthermore, he studies the effects of perioperative fasting and optimization of feeding behavior. He has a specific interest in the neurometabolic changes that occur due to surgical stress and the potential neurotoxic consequences.

Finally, he has dedicated himself to perform "appropriate research", as he believes that scientists should take scarcity of personnel, money and environmental strain into account when studying future treatments.

Did you know that...

... AGEM researchers **Anita Boelen** (Amsterdam UMC) and **Monique Albersen** (Amsterdam UMC/Rijksinstituut voor Volksgezondheid en Milieu) were interviewed by Laboratoriumgeneeskunde about the national screening of newborn babies? They talk about the history of the screening program, and about last year's pilot to implement the metabolic disease Adrenoleukodystrophy (ALD) into the heel prick test.

... newborn boys in the Netherlands will be screened for adrenoleukodystrophy (ALD), an inherited metabolic disease? Boys with ALD are at high-risk of developing adrenal insufficiency and/or cerebral ALD. Newborn screening for ALD enables prospective monitoring and timely therapeutic intervention, thereby preventing irreversible damage and saving lives. Amsterdam UMC has a key role in the screening and treatment.

... the SIMPATHIC Consortium, led by the Dutch Radboud University Medical Center and Amsterdam UMC, has developed a new approach to expedite the use of existing drugs for groups of patients with rare neurological disorders? The consortium has been awarded an 8.8 million euros grant from the Horizon Europe program to further develop this innovative method.

... brain responses to specific nutrients are diminished in individuals with obesity and are not improved after weight loss? "The fact that these responses in the brain are not restored after weight loss, may explain why most people regain weight after initially successful weight loss," says **Mireille Serlie**, Professor of Endocrinology and AGEM Principal Investigator.

... a new drug, investigated by Amsterdam UMC together with colleagues around the world in universities and the industry, is effective as a treatment against ulcerative colitis? With the clinical trial demonstrating a doubling in the rates of remission, to up to 50%, in certain groups. The results of this clinical trial are published in the New England Journal of Medicine.

... harnessing the power of endothelial metabolism could be a novel approach to reduce the atherogenic milieu in the bone marrow niche and atherosclerotic plaque? For this project, AGEM Principal Investigator **Jeffrey Kroon** received a prestigious ERC Starting Grant.

… AGEM researchers **Eveline Bruinstroop** and **Jeffrey Kroon** attended the EMBO leadership course in Heidelberg?

… **Carla Hollak**, professor of Metabolic Diseases, in particular hereditary metabolic diseases, at the University of Amsterdam and Amsterdam UMC, received the Academy Medal from Royal Netherlands Academy of Arts and Sciences (KNAW)?

… a new Nutrition Textbook was launched? The Nutrition Textbook helps apply knowledge about nutrition in prevention and treatment. It is aimed primarily at practicing and future doctors, dieticians, nurses and physiotherapists. The textbook is an initiative of four AGEM researchers: internist-endocrinologist **Maarten Soeters**, dietician-researchers **Nicolette Wierdsma** and **Hinke Kruizenga**, and gastroenterologist **Gerd Bouma**.

… dr. **Joep Grootjans**, gastroenterologist and AGEM researcher, has been awarded a NWO Vidi grant for his project "Abdominal cavity immune cells facilitate cancer cells"?

… drug rediscovery refers to the principle of using 'old' drugs outside the formal indications? The group of dr. **Nanne de Boer**, AGEM Principal Investigator, aims to visualize potential hurdles that hamper drug rediscovery in general, to emphasize the global need for optimal use and development of useful drugs, and to provide an overview of the registration process for thioguanine in the Netherlands.

… Dr. **Mirjam Langeveld** has been appointed as the new head of the section Inherited metabolic diseases, of the sub department of Endocrinology and Metabolism?

… Prof. dr. **Geert D'Haens** has been appointed as the new department head of Gastroenterology & Hepatology (MDL)?

… AGEM is involved in and at the forefront of the Amsterdam UMC-Food for Life initiative?

… Prof. dr. **Joost Drenth**, Dr. **Reinier van Hest**, Dr. **Bart Koot**, Dr. **Elena Levtchenko** and Dr. **Sybren Meijer** were appointed as (AGEM) PI in 2023?

… a grant of €9.4 million has been awarded by NWO to the MenoPause consortium, led by AGEM PI **Peter Bisschop**? The consortium aims to ensure that all women around the menopause and beyond remain as healthy as possible, and can participate fully in social life.

… patients suffering from Crigler-Najjar syndrome accumulate unconjugated bilirubin to levels that, if left untreated, will cause irreversible brain damage? The results of this study were published in NEJM on August 17th 2023.

… a number of researchers of Amsterdam UMC have again been awarded a TKI-PPP grant between € 300.000 and € 750.000 to perform a research project in collaboration with an industrial party? Dr. **Maarten Soeters** received a grant for his PEARLS project and Dr. Bruno Sovran for his MICROPIAL research project.

Future perspectives

As we look ahead to 2024, the AGEM directors prof. dr. Anita Boelen and prof. dr. Stan van de Graaf, are enthusiastic about the upcoming changes and opportunities of the new year. The most imminent change will happen right on January 1st, when, after nearly eight years, prof. dr. Stan van de Graaf will step down as AGEM director. He will be succeeded by dr. Nanne de Boer, gastroenterologist at the department of Gastroenterology and Hepatology. “Although this signifies the official end of an intense and highly interesting period for me, I am excited to pass the baton, especially since this will once again bring a clinical perspective into the directory!”, Stan smiles. “I will miss the seamless collaboration I had with Stan, but he definitely deserves it to finally focus more on his research”, Anita adds, “and I am confident Nanne and I will make as good a team as any”.

Not only will Nanne have big shoes to fill, there will also be big steps to take. The year 2024 focusses on turning the recommendations from the SEP evaluation into concrete strategic aims. “While we have only received preliminary feedback, we are confident that the final report will include valuable insights and practical recommendations.”, Anita explains, “so, we look forward to reading it next year.”

“In the meantime, there are some things we already have on the agenda”, Stan says, “for example, building on the success of integrating the Food for Life theme in our strategy, we will continue in 2024 with a new converging theme, namely Advanced Diagnostics.” “We will organize a PI event, focus the 2025 AGEM Innovation Grant on this theme and possibly organize a symposium”, Anita adds.

This aligns with the overarching objective of organizing more events to facilitate networking and to enhance the AGEM community spirit across all levels, with a particular focus on early-mid career scientists through Young AGEM. “We hope this will result in more collaboration between AGEM researchers, departments, and research institutes, and possibly even the formation of new public-private partnerships”, Anita emphasizes. “The research we undertake has a clear societal benefit, and I am confident this last part could become a reality, especially with the support from our business developer Ric van Tol”, Stan adds.

Finally, AGEM will continue to organize strategy meetings with all the department heads affiliated to AGEM, with the objective of uniting the vision of the future of the institute and its researchers. “I hope this will result in a two-way street”, Anita says, “It is my hope that the departments will also begin to see it as a logical step to involve AGEM and other research institutes in their own strategic aims”.

“All in all, we look forward to a year with more connection, more collaboration and national fame!”, Anita concludes with a smile.

Stan van de Graaf, AGEM director
Anita Boelen, AGEM director
Eva Dirkx-Beuling, AGEM policy officer
Esther de Regt, AGEM policy officer

MSc. Esther de Regt, Prof. dr. Anita Boelen, Dr. Nanne de Boer and Dr. Eva Dirkx-Beuling

A word from the next AGEM co-director dr. Nanne de Boer:

"I cannot wait to start building on the foundations that were laid down by my predecessors. I would love to create an even bigger name for the institute and increase the sense of pride and belonging among the researchers that are already part of AGEM. I am confident that the younger generation will play an instrumental role in further enhancing the value of the research institute as a whole."

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